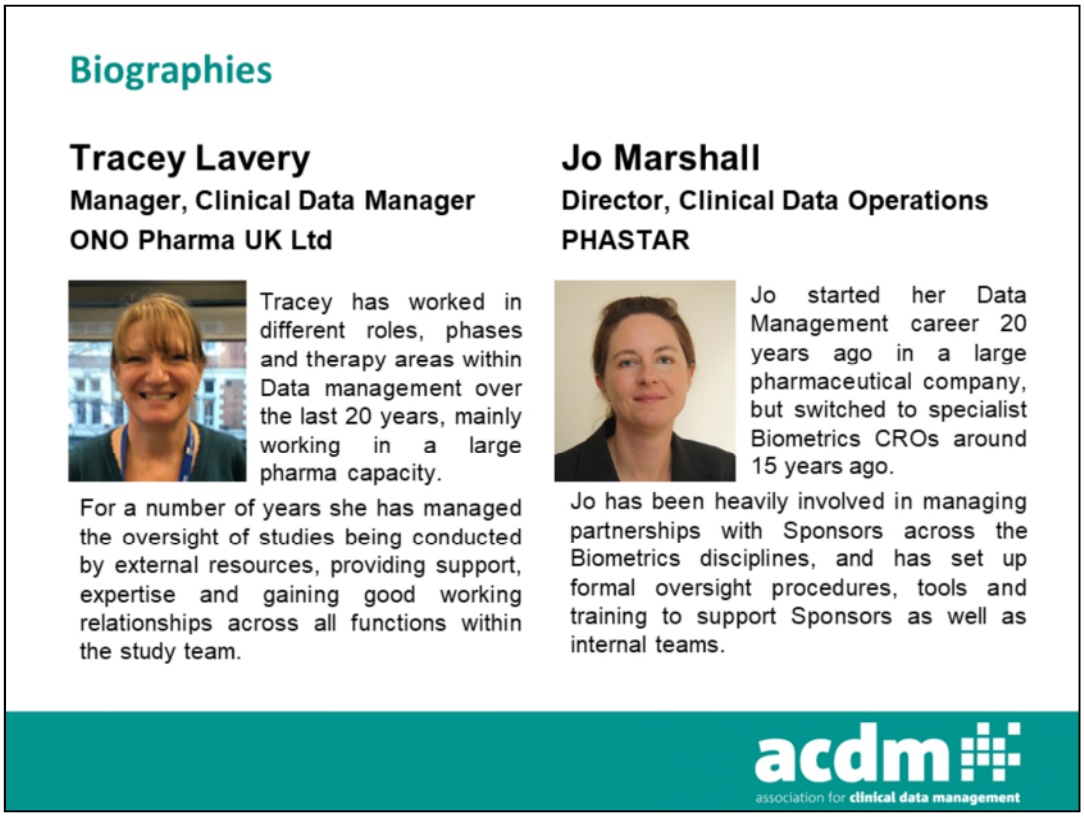
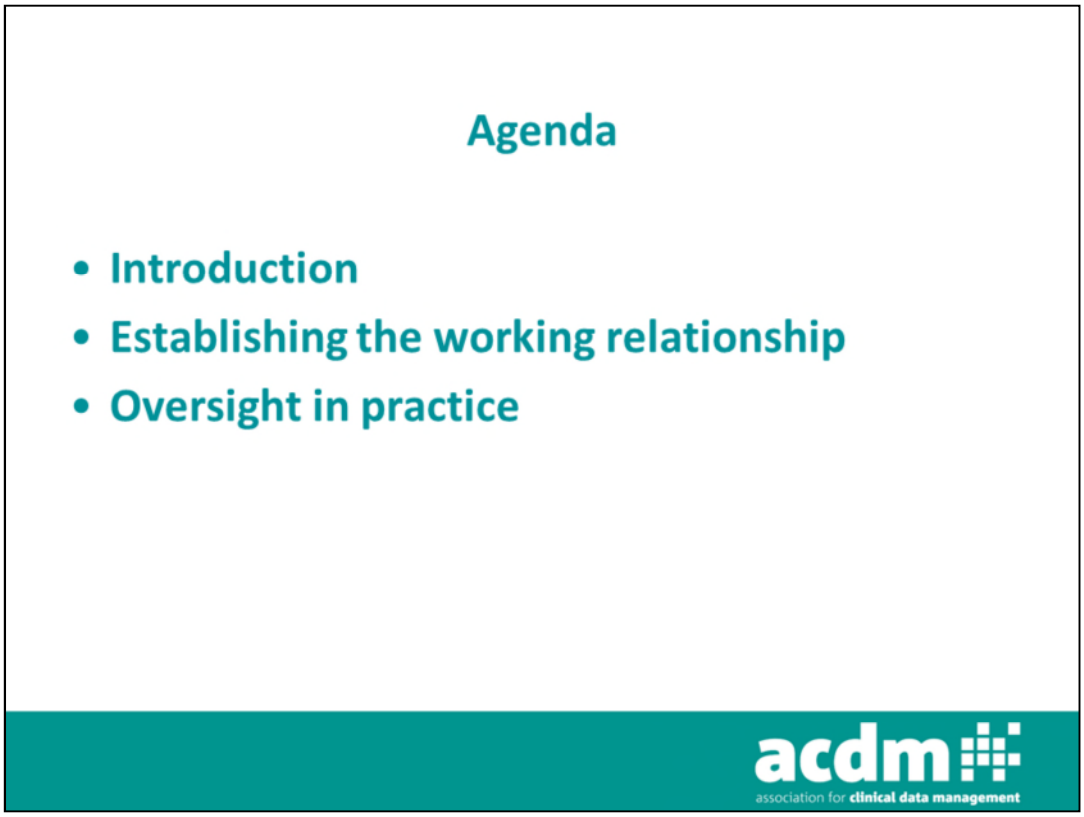
Welcome to this webinar on building Data Management success within Sponsor and CRO relationships.

We are here today to go through some information and recommendations of building success into your project Data Management from both Sponsor and CRO perspectives.

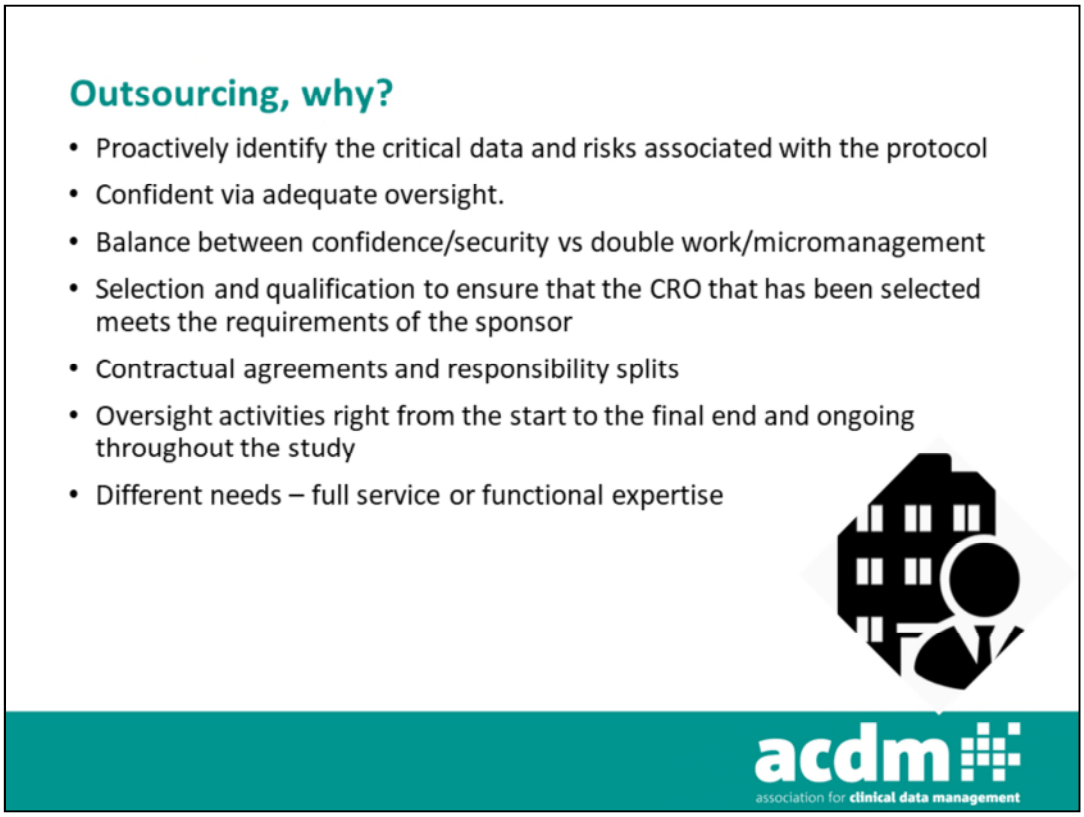


Tracey Lavery has been in DM for a number of years and her current role is to manage the oversight of our outsourced studies. She has over 8 years experience working with full service, part service and functional expertise outsourcing and each one has its different requirements and challenges and one thing we have learnt is that building a good relationship is key.

Jo Marshall brings the CRO perspective to the webinar. She has always worked for Biometrics specialist CROs and been a major part of not just creating proposals for Sponsors, but also creating the standard tools needed to generate those proposals. She has also created and deployed solutions for providing vendor oversight as a service to Sponsors particularly where those sponsors don't have the inhouse capability expertise to do this themselves. Working with a Sponsor to get the scope of work accurate are the building blocks to a good ongoing relationship.



During this webinar we are going to give an introduction to this subject and then talk about establishing working relationships and oversight.



The primary reason for a Sponsor to outsource clinical trials to a Contract Research Organisation (CRO) or external service, is that they may have limited internal resource or lack experience with in the disease group being targeted. Biometrics including Data Management is a popular choice for outsourcing as it involves processes and systems that companies may not have internally or want to invest in themselves and involves a number of repetitive but discrete tasks that can be completed by third parties relatively independently.

Key Points to consider (Sponsor):

- The sponsor should aim to partner with a CRO early to proactively ensure the data and risks associated with the study/protocol are identified and addresses with the data in mind.
- Sponsor needs to feel confident they have adequate oversight of the CRO and a balance between confidence and security vs micromanagement or duplicating work in house, we will talk about getting your data management oversight right later on.
- Selection and qualification to ensure the data management CRO has been selected meets the requirements with good contractual agreements and responsibilities.
- Oversight from start to end and ongoing throughout the study to confirm the CRO continues to meet the sponsor's requirements and the data integrity is as expected.

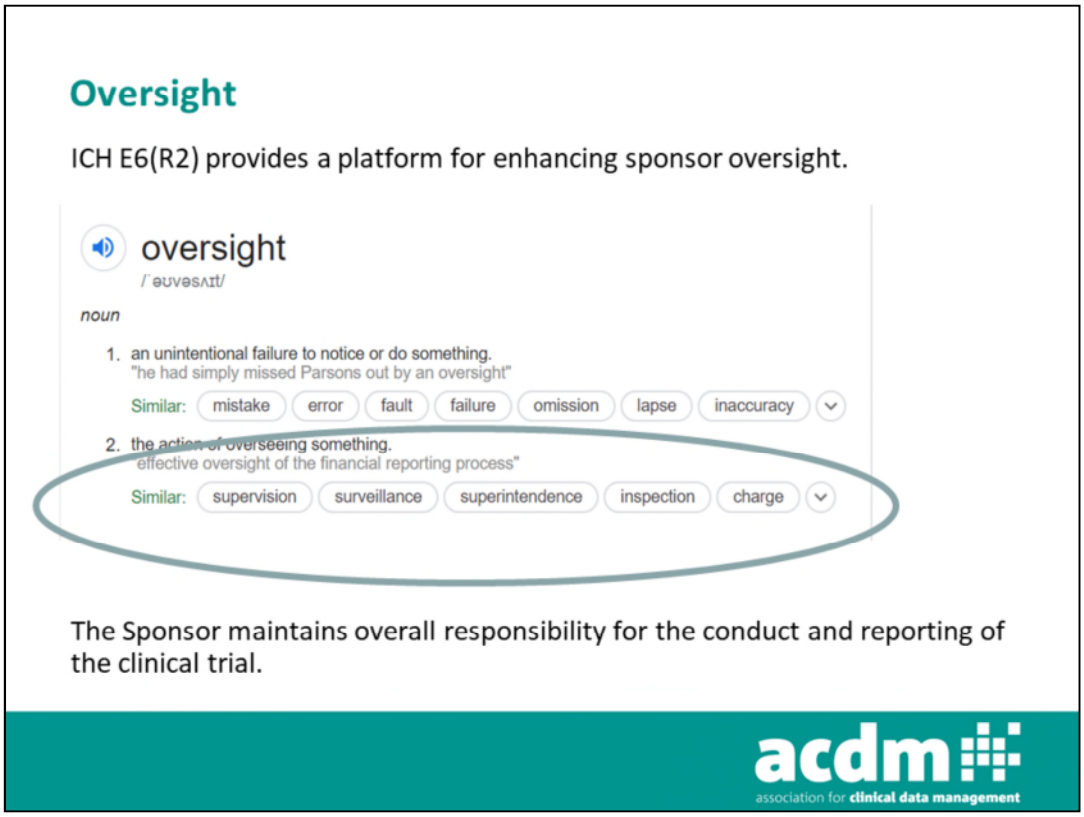
Key Points to consider (CRO):

- Provide a robust proposal with as many assumptions as possible, show case

your ability to meet the requirements and open up discussions.

- Have the confidence to propose good practices and experience based around knowledge and lessons learnt.
- Ensure the scope of works clear and all components and activities meet each functions expectations
- Meet the oversight activities with a positive approach in order to work together with your Sponsor.

We will go over more of these points during the webinar.

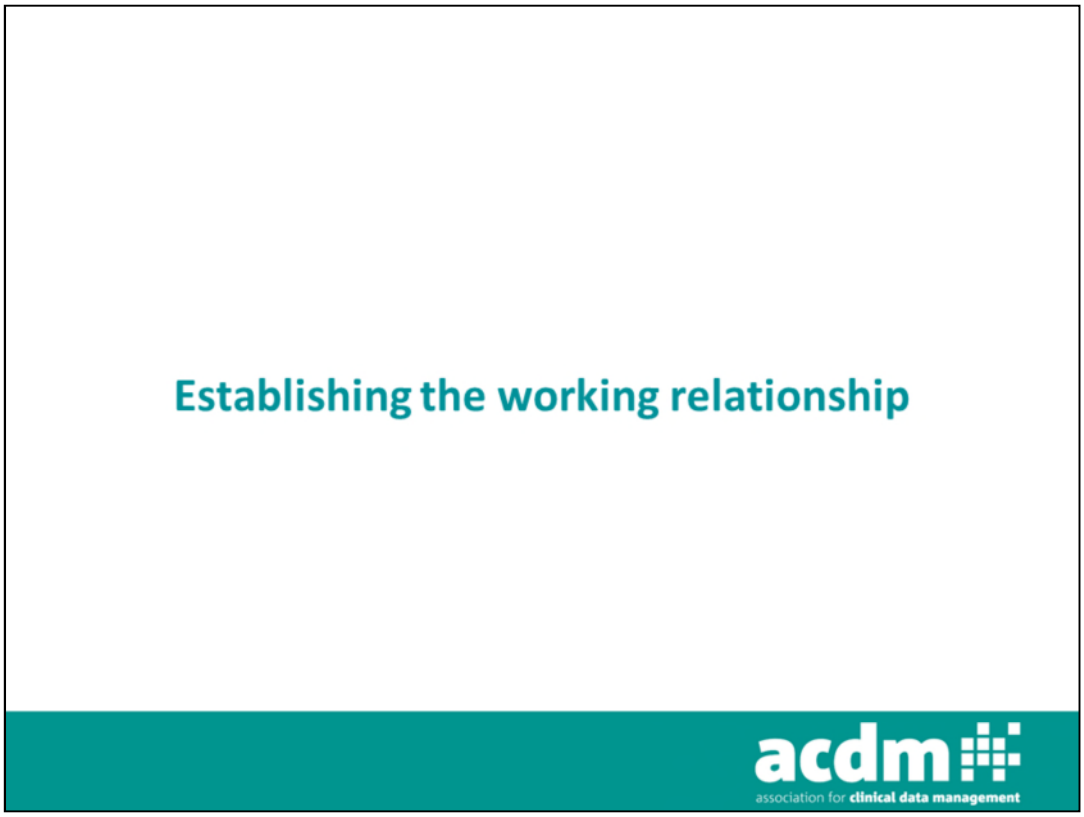


h the integrated addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6(R2) an additional requirement under section 5.2.2 that states 'the sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO's' (Clinical Research Organisation).

Oversight meaning in the dictionary – the action of overseeing something.

As the Sponsor maintains overall responsibility for the conduct and reporting of the trial, there should be mechanisms in place to demonstrate oversight of activities contracted/ delegated to ensure patient safety and data integrity. The CRO should work with the Sponsor to ensure they support this oversight effectively.

This addendum has given opportunities for both party's to outline the expectations, clear lines of responsibility, transparency and develop good working relationships.



There are a number of steps that go into a working relationship before a contract is even awarded. These steps are really important to get the expectations right and to ensure that everyone understands exactly what is required.

Matching up the right CRO with the right Sponsor can be full of pitfalls, and until two companies start working together how do they know whether the relationship is going to be successful?

CROs should assess their ability to successfully deliver a project before they provide a proposal for the project. Sponsors need to critically assess that quote and any additional evidence to determine whether they believe the partnership will work, this due diligence will ensure any relationship starts in a transparent way.

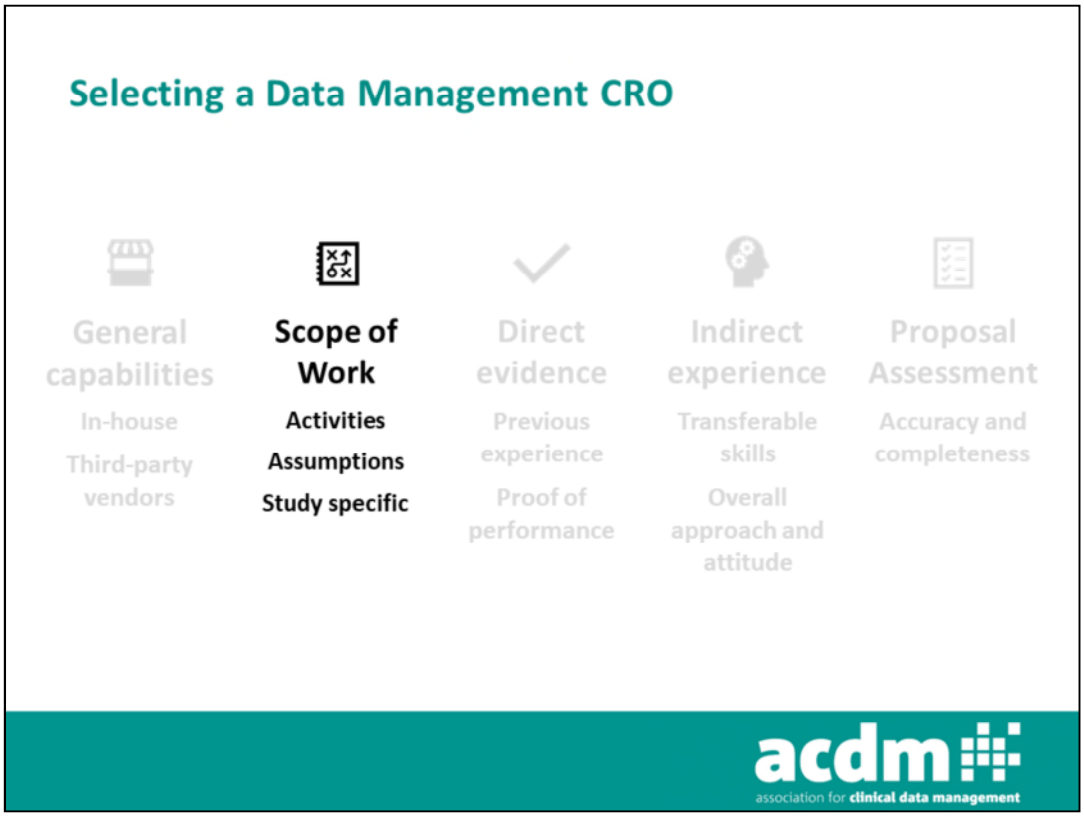
Take a look at the general capabilities of the CRO, do they have the capability to perform the service, do they have the right systems in place, do they have the right partnerships with appropriate vendors?

Can they conduct all items required by the Sponsor? Do their processes cover all the data management aspects that you expect to be covered?

Are those conducted in house or via third-party vendors? Bear in mind the type of biometrics vendor you are looking at here, if you want a specialist biometrics vendor then it is possible they will work closely with vendors on some aspects, these relationships can sometimes be just as effective as different departments within the same company, so if they are through vendors, how established are those vendor partnerships? I worked on a project with a large CRO doing the clinical function and us as a specialist biometrics CRO doing the Data

Management, and the project manager admitted that they had a better relationship with us than they did with their own DM team who they hadn’t worked with very much and were based elsewhere in the world.

Many companies will capture this information by including a Request for Information either before you request a proposal or alongside the proposal request.



The scope of work is a very important document to frame the expectations for the study and ensure that the requirements are interpreted in the way you need. The more accurate the Scope of Work the more similar the proposals are likely to be, however detailed scope of works can also provide challenges for the CRO to complete.

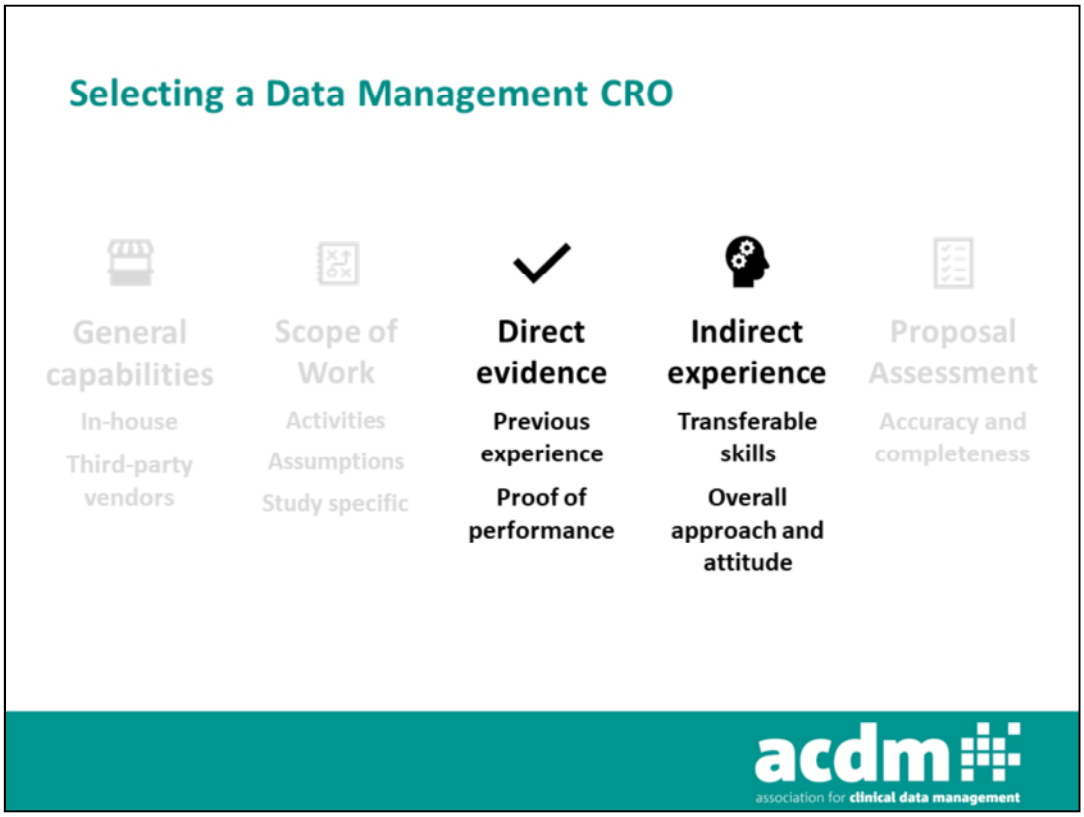
Sometimes the SOW's are created and distributed without full DM input, or the sponsor DM function is not consulted prior to finalisation, most SOW's are often pulled together by a different department and they are not experts in the day to day running of a trial, they will be basing it on the information provided by the study team and it some cases the draft synopsis. SOW's are templates and don't always distinguish types, phases and complexity of the trial, therefore the CRO might need to highlight missing components based around their experience or ignore parts that clearly don't relate to the trial.

There are some areas definitely worth reviewing for study specific accuracy - Assumptions can vary significantly between vendors if not agreed upfront by the sponsor, however not all assumptions are interpreted in the same way even if they are provided by the sponsor. A good example is the assumption Number of queries per patient, if this is provided by the sponsor is their measurement the same as the CROs measure? Are all the CROs interpreting this in the same way. If you are provided with an assumption of 100 queries per patient, is this just the queries that require data management intervention to resolve, or does it include discrepancies firing in the eCRF and being resolved at the point of entry?

Less detail in a scope of work can sometime cause issues as well, resulting in a number of questions that require clarification, so it is a good idea to build time for this into the processes. Often the detail is not clear, for example, there is not enough information on third party data, which of the data in a synopsis is to be transferred electronically, how often, do you want it to be displayed in the eCRF or reconciled outside, how do you want it transferred, how standard is the data, how established is the vendor.

Other typical areas for misinterpretation are results from vendors, for example PK results maybe needed during a safety review meeting for a dose escalation but it isn't clear how the results are being provided to the sponsor. Are the results being delivered directly to the sponsor from the lab and then sent to the CRO to be added to the whole data or is the CRO receiving the results and delivering it with the agreed datasets for the SRC. These decisions have an impact on time, cost and resource and are nearly always out of scope.

Having a synopsis is really important for an accurate proposal, it allows calculation of the number of pages to build and process, and how many are non-standard etc. It allows estimates of other assumptions that may not be directly provided by the Sponsor and minimises the questions a CRO might have.



Direct evidence and indirect experience:

Look for direct evidence of the CROs previous experience, and proof of performance, balance that with the experience and requirements of the Sponsor. A sponsor experienced in a certain area may be able to support a CRO in that area if they have particular expertise elsewhere. Consider Data Management experience separately from the Clinical, there are advantages in placing Data Management with the Clinical provider, but this may not always be the best approach.

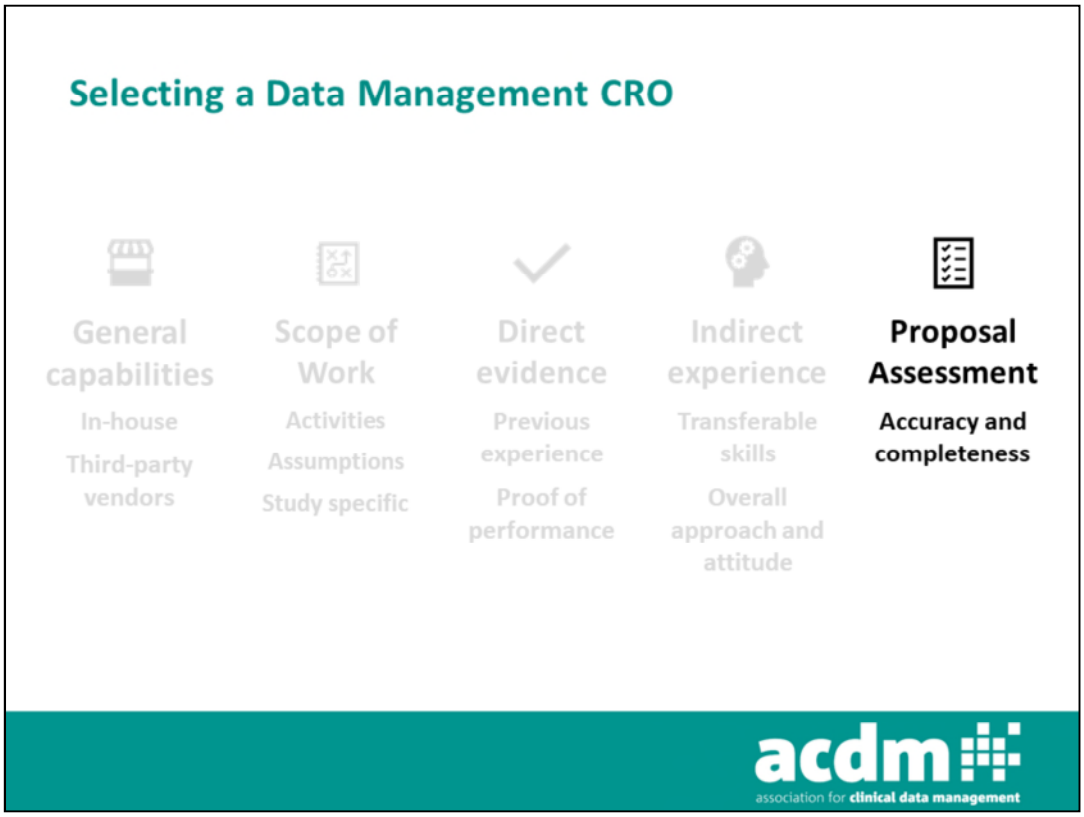
Ask for evidence of the claims, and assess that through an audit, but don't dismiss a CRO if they don't have the direct evidence you expected to see, look for additional evidence as to whether they can do what you need. Transferable skills are important, it may not matter that they haven't done the specific thing you are looking for before if they have the ability to work well with you to define and execute the requirements together.

With regards to assessing the technology, ask how many studies has the technology has performed, and what is the CROs experience with the technology? Its worth asking practical, detailed questions such as where the is data stored and what are the back-up procedures, How is access managed? How is the tech supported, in terms of what will the CRO do and what will the

vendor do. Ask what the biggest risks are with this technology, and what are the mitigating actions?

Make sure any technology to be used is fit for purpose, spend the most you can afford if you have a choice. Don't be afraid of using technology that you are not familiar with, many sponsors are missing out on some good advantage of newer technology because they don't understand it properly or they think the expense is not worth the benefits, but the pricing is generally driven by what the technology is worth and the CRO will help you with the technology to make sure you get the most out of it. Check whether the technology is off the shelf or bespoke, cloud based or on the CROs servers, whether it is configured for the CROs requirements or used as is. CROs validate based on these main points, with the amount of validation required increasing with the ability to affect the functionality of the system. For all DM specific systems you would expect to see performance qualification, you may also need installation qualification and operational qualification if any configuration or bespoke product.

Sponsors often will stick to what they know, for example EDC/ePRO/CTMS as staff are trained in those systems or they own URL/specific portal for the systems. Validation of Technology being provided by the CRO would be conducted as part of due diligence pre-award and the sponsor may request a test or training area to take a look, along with certificates, SOP's and any working guidelines associated with it.



Questions to be considered include:

Take time to assess any proposal properly to ensure the assumptions are correct, and that both parties are clear on what is included. Also check the expectations for each task, are aligned? For example the task ePRO set-up, might mean managing the design, build, integration and UAT of a patient diary experience for one company, but for another it might just cover the import of the ePRO data from the ePRO vendor into the clinical database. It's particularly important to do this before you sign any contract, to make sure both parties are aligned on their expectations before you start.

Drilling down on DM costings using bid grids or similar task listings are a good way to highlight what is involved, what is required and also what might be missing/expected. However it can be a challenge to fit items into a bid grid, for example hours per item or unit costs. The tools used to create proposal often don't map well so the tasks have to be split over several items in a bid grid, and then it is a bit of a guess on how much to put where. Or tasks involve different roles for different amounts of time so you can't say that one person does a task at a specific rate, this means the unit rate on a task is often a blend of the different roles involved based on the proportion of their involvement. This can result in Sponsor's struggling to understand the costing algorithms used to calculate the cost, as they have the tasks and costing associated with the task but not the algorithm used to provide the cost or not adequately explained using a key or unit

pricing. Having transparency of rates and hours doesn't necessarily help as there are so many variables that go into each of these that they can vary significantly between companies, so probably are not the best measure to use.

So for both the CRO and the Sponsor it is helpful to be clear on the definitions of assumptions, and if you use one, allow flexibility in your bid grid, accept that using a bid grid will increase inconsistencies particularly between grids and subsequent change orders. Work out a level of transparency that works for the CRO as well as the Sponsor, don't get into the detail, instead look at the plausibility of the proposal and comparisons between proposals, based on detailed assumptions, but cost at a high level.

Other Sponsor issues can be:

They are not always the expert on what is required and may need some guidance from the CRO as to what is the minimum requirements are.

The proposals are normally built on line items so that each task/item is costed for example eCRF specifications, *medical coding, Database transfers, vs external data, interims/IDMCs/DSURs , EDC user management and local Labs, etc..

Number of unique and repeats modules are the biggest drivers for set-up, along with number of non-standard pages. So I would usually expect between 25 and 40 unique pages although clearly depending on the complexity of the study this might change – it is closely linked to the number of assessment on a schedule of events. Repeat pages will depend on the number of visits so can be highly variable. The biggest drivers for cleaning and locking will be the number of pages, the number of medications for coding, SAEs, number of queries, amount and type of third party data, number of EDC users, number of interims or IDMCs as well as the technology used.

Make sure you allow enough time for project management activities for the Data Management team, for example communication and meeting attendance can add up to quite a lot, but not enough has a big impact on the success of the project including potentially increasing time due risks being realised, rather than being mitigated through a good communication schedule.

So, the selection has been made, the contract research organization – CRO – that best fits the Sponsors goals, timeline and budget is in place. What's next?

Ensure that neither party underestimate resource needs, particularly from the sponsor side. It's a mistake to think that it's "all in the CRO's hands" and that few to no sponsor resources are needed.

There is a balance between micromanaging the CRO and taking a totally hands-off approach. It is vital to the success of the project, that the sponsor should have a dedicated resource to work with the CRO.

Once the contract and work orders are signed, the first order of business is to confirm and document the roles and responsibilities of each party in detail. The right balance comes from the CRO and the sponsor being comfortable with the established roles and responsibilities and trusting each other to independently perform as agreed. Some tasks, like specifying the eCRF need to be a collaboration, especially if a number of non-standard forms are used, others will very clearly be split to either Sponsor or CRO.
Setting the expectations for each task is also important, the both parties are aligned and working to the same goals. This is often overlooked in favour of a simple responsibilities grid, an approach that is likely to cause issues as the project progresses.

A kick-off meeting with all study team members is the perfect time to do this.

Some of the questions to resolve may include:

Who is leading the project? Thinking proactively, anticipating next challenges, and proposing next steps?

Who will be leading team meetings and issuing meeting minutes and action items?

Who is responsible for driving the completion of action items?
Who is responsible for communication?

Who is responsible for ensuring the different tasks are is on track? For example enrolment may not be a data management task, but quicker or slower enrolment can have a significant impact on data management activities and therefore should be monitored by both parties in order to manage a collaborative approach to potential solutions if changes occur.

The above questions form a good basis for understanding of the project and expectations, this works both ways.

DM is often a discipline that is resourced to more than one project/study. Within the Sponsor this could be a percentage of time per FTE as the project or study is from an oversight capacity, as from the as from the CRO a resource will also usually work on a number of studies, depending on the study size, as this builds in redundancy to a study and makes sure that enough resources are familiar with a study

As with any relationship, clear and frequent communication is the key to a productive, collaborative, and effective sponsor-CRO partnership.

Establish your preferred method of communication at the start and be willing to adjust as challenges and opportunities arise. Be clear about what and when to communicate via phone call, versus in a meeting, or in an email.

If you, as the sponsor, are not satisfied with any aspect of the CRO's performance, no matter how small it may seem, don't hesitate to voice your concerns. The earlier the better! Resist the urge to just fix it yourself. It is your responsibility to ensure that you understand the situation and provide constructive, relevant, timely feedback to your CRO. In return, as the CRO, if anything is causing particular problems, discuss it with the Sponsor at the earliest opportunity to give yourselves the opportunity to improve or change the situation.

Have a good clear escalation process, with different levels/personal to ensure the correct members of the team are included in discussions. This can be used to avoid panic and blame.

Each project typically has a scope or scheduled of works/tasks that should be created to ensure that all parties are fully aware of the project, the tasks involved and what is being preformed by the CRO and the Sponsor, we discussed this earlier.

It's also a good idea to develop a document to outline the expectations similar to internal ones, for example a 'Task Accountability Matrix' or a RACI (responsible, accountable, consulted, informed).

Communication Plan and issue escalation process

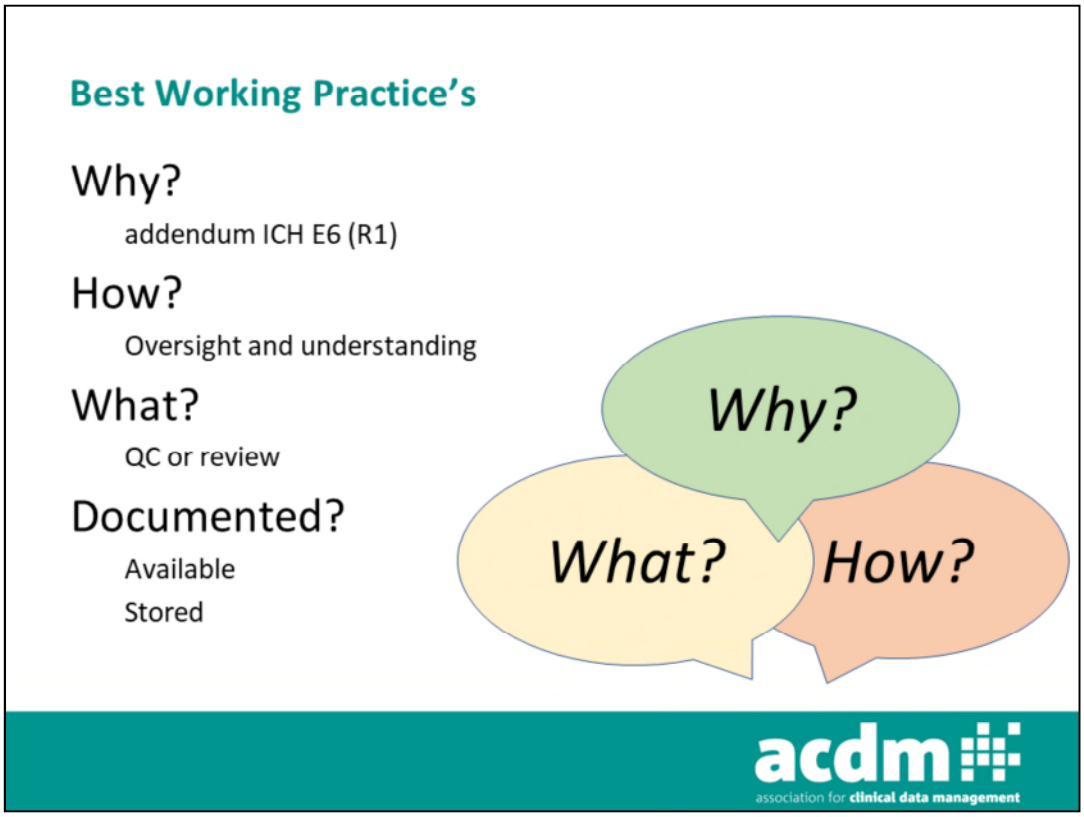
Decide on what process should be followed and who's – will the CRO be following their Standard operating procedure's (SOP) and if not which ones should be shared by the sponsor?

Same with templates. Is the CRO using their templates or the sponsors? Bear in mind that unless this is established at the proposal stage there will likely have been an assumption made in order to be able to provide that proposal.

Timelines also need to be agreed and maintained, is this done by the CRO or sponsor?

Access to systems or areas where documents are to be stored. For Data Management this includes determining what access is needed to the EDC system, and whether additional reporting will be needed on the data and progress of the data cleaning for example.

If you are planning to build an ongoing partnership then having a high level document could save time duplicating the above tasks, for an example a ‘Working Guideline’ or ‘Handbook’ would list all the typically tasks, expectations and responsibilities, etc. for all projects. This could have a study section where study specific requirements are added but the basis of the document would stay the same.



As the project/study has been outsourced it is not always easy to access the data or control the work being done at the CRO. A good level of Trust is needed along with a good working relationship, but oversight is the sponsor's responsibility and it is up to them to demonstrate oversight of activities contracted/ delegated.

Why? As we have already mention with the integrated addendum ICH E6 (R1) the additional requirement states that 'the sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO's' (Clinical Research Organisation).

How? The sponsor needs to document the oversight and have a clear understanding of what is happening with the project/study. There should be a clear level of oversight and what detail is required, this could be an action log or meeting minutes.

The sponsor should not be duplicating the work being conducted by the CRO but should be aware of their process's, the risks and issues in the study and overall oversight.

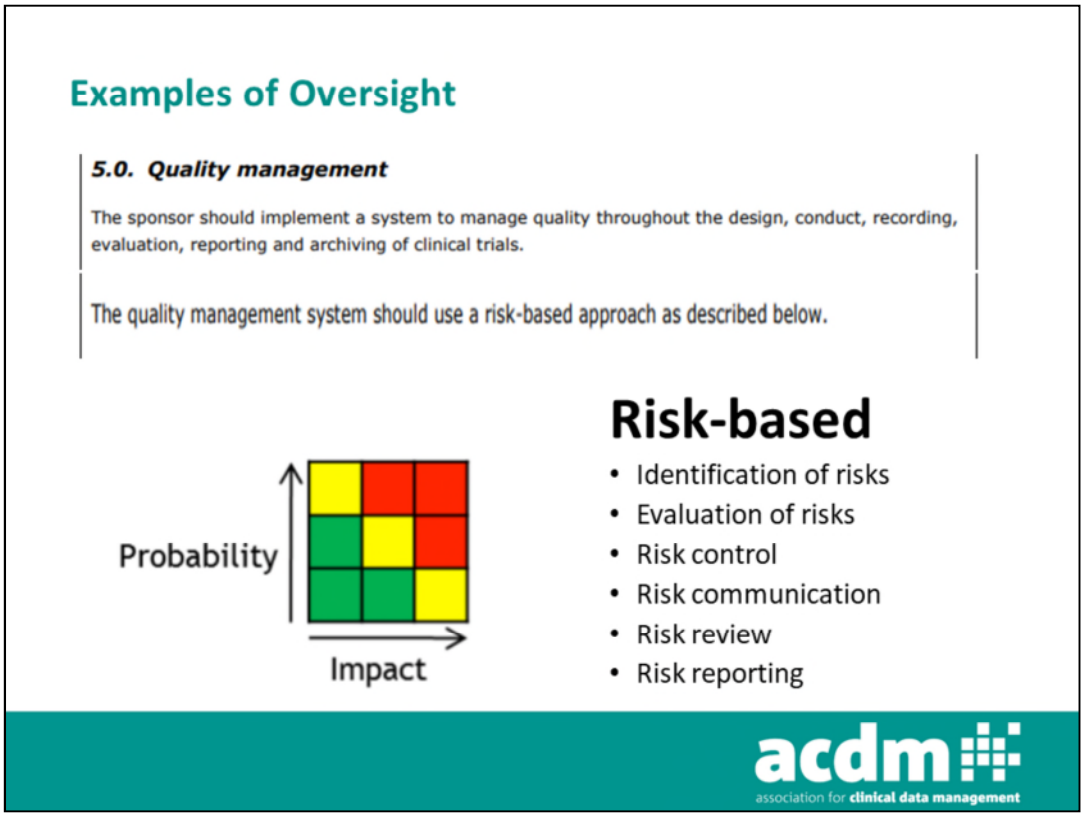
What? Some sponsors have developed an 'Oversight Plan' which defines what is required, provided and documented by the CRO and what is being reviewed and documented by the sponsor.

Depending on the project, relationship with the CRO and complexity it should be agreed what tasks, documents or data should be QC'd and how often.

Documented? The oversight needs to be documented and stored in the trail master file (TMF).

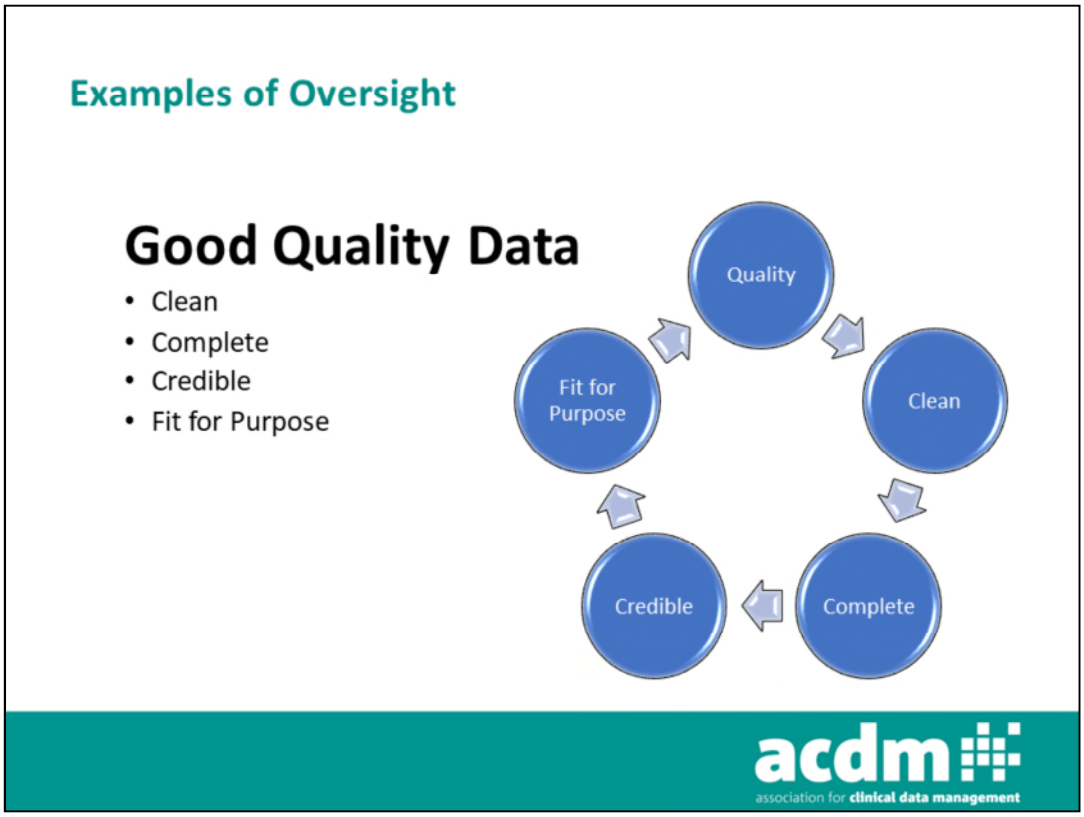
This can be a QC of the CRO's TMF, follow the process for reporting SAEs, good management of actions, decisions or issues identified in the project/study and the quality of the data being provided meets expectations.

Oversight in practice



ICH E6(R2) says that the Sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of a clinical trials, and that quality management system should use a risk based approach.

This can be applied to the oversight requirement that the Sponsor has, and the Sponsor and CRO can work together to identify risks that will impact the data management activities, evaluating them to ensure they are graded appropriately based on the likelihood of occurrence, the impact of the risk should it occur, and the ability to detect the event happening. The Sponsor would then plan their oversight activity based on the highest risks, and work with the CRO to identify ways to monitor those risks together. Making this a collaborative approach means that both parties buy in to the need and are invested in ensuring the oversight is effective.



Quality of the data being provided meets the expectations of the team. If access to the data is available it's a good idea to run some of the available reports (if EDC) and check that data is being reviewed, queried and corrected in a timely manner.
Quality of the data being provided should meet the standards expected and if not this should be something that is discussed with in the study team first and escalated if re-occurring. Make sure you know what expectations you have of the data quality, and consider how you would measure, this which is now commonly part of risk based quality management.
Establish standard practices that produce 'fit for purpose' data sets, i.e. quality data. Fit for purpose methodologies imply that data quality improves when the data collected becomes more targeted to the study objectives.
Eliminating non-critical data points lowers risk during endpoint analysis and minimizes the effort required to verify non-critical data.
Remember the sponsor should not duplicate the work of the CRO, but can request access or listings of data, queries or outputs to review the quality of the data. Findings should be documented and fed back in a constructive manor to the CRO counterpart, for example the CRO Data Manager who will follow-up and provide an update.

Cleaning of the data should be ongoing on an appropriate schedule and tracked so the Sponsor can monitor it's progress.
Complete data is very important and should be monitored closely, if data is missing then it can't be cleaned and could lead to missing import data cut off's or

interim analyses.
Credible data is a must for the integrity of the trial or study being conducted, statistical monitoring methods can be very helpful in assessing the credibility of data, particularly for larger datasets.
Fit for purpose data is required to prove the investigational product is a success.

QC of the CRO's TMF along with the Sponsor's own is an important part of oversight, as this ensures that you are inspection ready. Even though the CRO is creating and storing the documents for the study in their TMF, it is still the sponsor's responsibility to ensure they are filed in a timely manor. This can also reduce the level of QC at the end of the study when the TMF is transferred to the sponsor.

It's a good idea to familiarise yourself with the CRO's processes (SOP's), especially Database lock, Change control, SAE reporting, etc.. These should be listed in the data management plan or similar document and can be requested if concerns are raised or quality is not being met.
As an example following the process for reporting SAE – identify an SAE and follow the process to ensure it was correctly and timely reported and followed-up. Other things to check could be alerts are going to the correct individuals and reconciliation is being manged timely, etc.. This type of "Deep Dive" can be conducted based on the risk involved in the specific processes and your identified priorities.

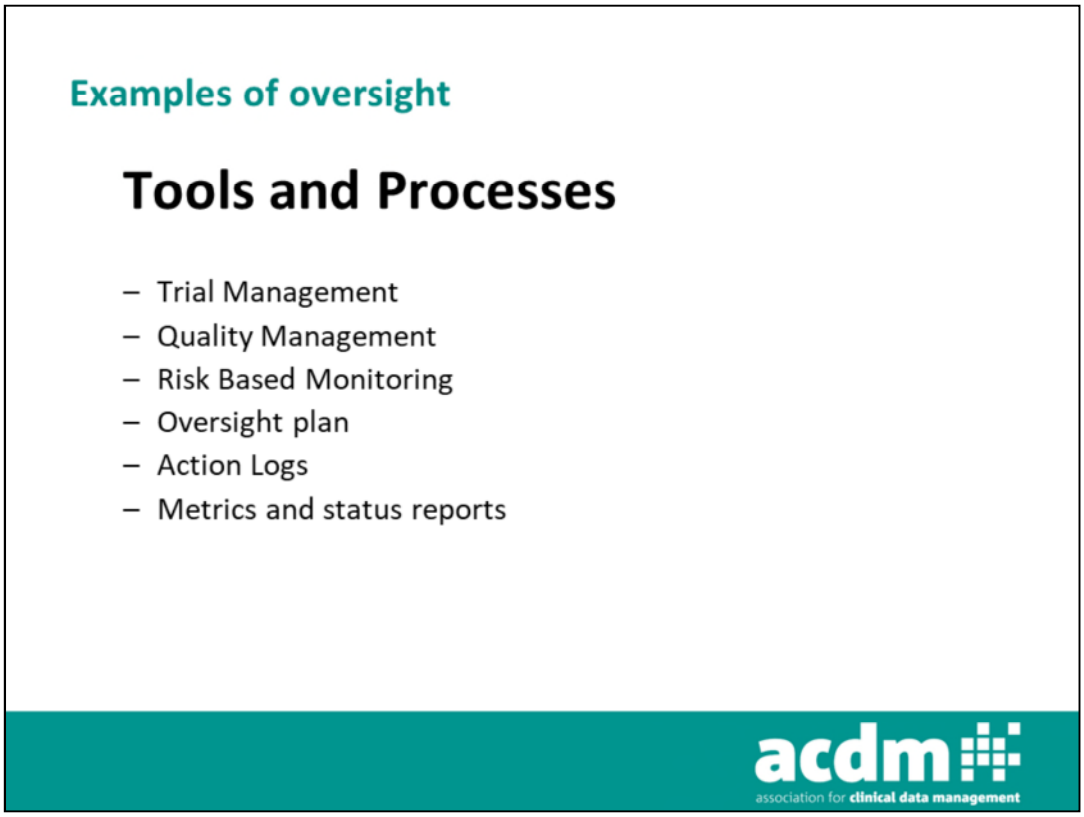
Project meetings and metrics are a good indicator of how the study is going, when queries jump up or data is missing for example, it should be discussed. Increase in queries could be down to a level of understanding by the site as to what is required, but it could be a indication of incorrect data points in the CRF. Missing data or data not being entered in a timely manor could be down to site

staff availability or complicated entry that needs some assistance.

As a Sponsor these need to be discussed and documented in the meeting minutes or actions logs to prove oversight of the issues and how these are being managed by the CRO.

Reconciliation of external data should be completed as per the agreed frequency, as a sponsor you should be aware if this is not be conducted in a timely manor, have a knowledge of the mismatches and queries being raised.

As a Sponsor these should be discussed and documented in the meeting minutes or actions logs to prove oversight of the issues and how these are being managed by the CRO and the external vendor.



As mentioned throughout this presentation tools and processes are key to success of a good working relationship as well as the projects or studies being conducted.

It's a good idea to frequently revisit action log and risks & oversight plans to ensure that any changes are documented or re-evaluated, along with any new issues/risks identify.

Trial and Quality management systems can be used to manage the challenges associated with running a clinical trial.

As an example, COVID-19 has had a major impact on the design, conduct and analysis on clinical trials and this has lead to several regulatory bodies releasing guidelines on how to handle various key factors.

This pandemic has not only affected the continuation/initiation of clinical trials, but also protocol amendments, informed consent, visits schedules (including screening process), monitoring visits, data capture, study reporting and investigational products distribution. The need to identify new risks, amended plans, record deviations from SOP's and processes and even shift to new technology has become important now more than ever. This is where a good working relationship and structured is really important to deal with unexpected issues together.

Action Logs, Metrics and status reports are a useful method of keeping track of issues and the trial progress, not just to provide an account to the Sponsor but reviewing logs running these reports can highlight things that are not easy to spot in a single form, patient or a result.

Most don't use metrics effectively, they feel like they are being judged, rather than being useful. Best metrics for collaboration are ones that measure the study, not the vendor.

Sponsor oversight of subcontractors if DM service providers use subcontracts these are mostly for technology. Ask for evidence of audit, include actions, metrics, milestones etc for those vendors in the primary vendor logs.

Given the highly important nature of data integrity as a fundamental of ICH, sponsors focus on DM systems and processes and integration when doing their due diligence as part of the CRO evaluation before award Too often the DM and stats are bypassed as the study is given to the CRO with the most preferable clinical approach. Consider the DM and stats in their own right, consider separating them from the clinical as that builds in oversight of the clinical vendor and encourages an environment where the Sponsor is more aware of the issues across the services.

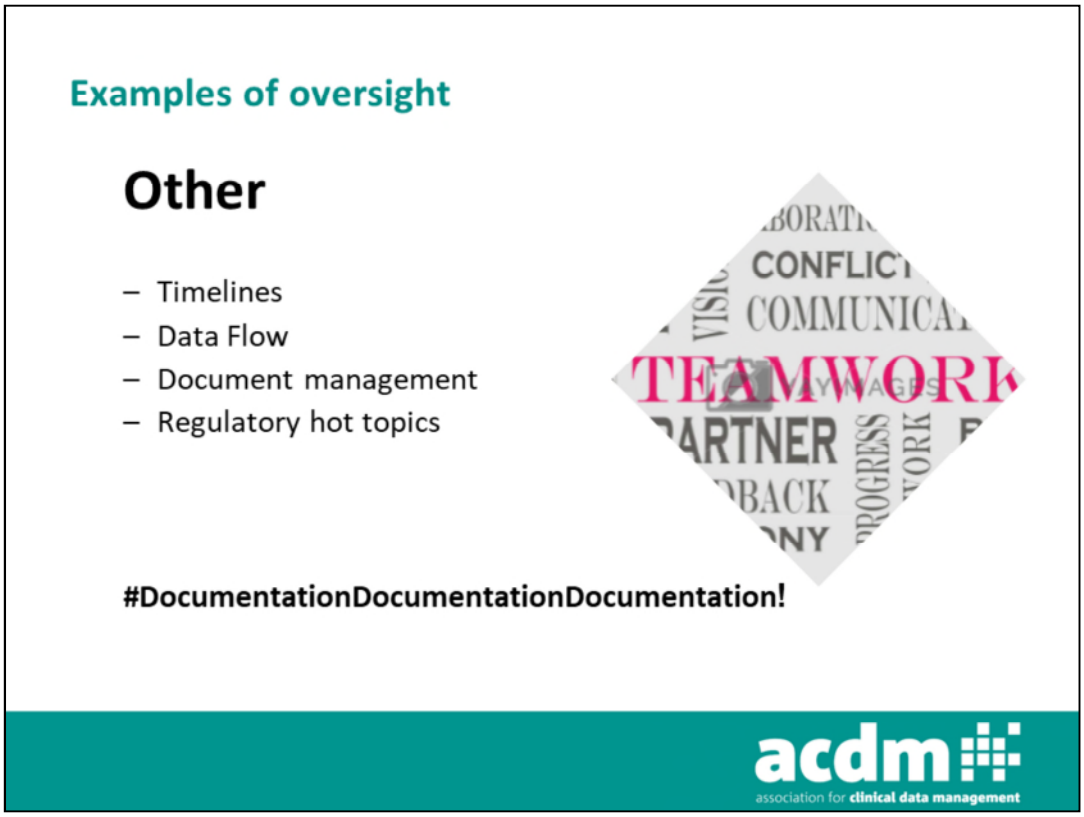
Use metrics & KPIs, not to measure failures, but as a tool to manage risks and highlight potential need for action

This hasn't always been a strong point within the Sponsor, as study level metrics are often provided by the CRO's DM team and there hasn't been the need to duplicate this in the past, however with the increasing need to prove oversight it has become more important to find ways of creating high-level project oversight metrics and not just key performance indicators.

Some independent companies have come up with industry type metrics that can be applied to any study or project, these use typical timelines (FSI, DB go-live, DBL, etc), task driven (Protocol, SAP, CSR, etc) and status driven (queries, clean pages, coded items, etc).

It's a good idea to ask the CRO to suggest what metrics they have available to provide evidence that the study is progressing as expected. Its also worth including these type of questions to the initial technology and evidence request, you don't want to be asking for unrealistic metrics or listings that the CRO can not provide.

Some companies (Sponsor and CRO's) have developed additional tools to track the cleaning status and these can provide visual outputs which can be shared with the study team.



Timelines are very important and should be monitored carefully.

Good understanding of the data flow between systems and vendors, data flow maps can be a good way to visualise the flow and again identify gaps and understanding.

Good document management of actions, decisions or issues identified in the project/study. Review logs or trackers to ensure they are kept updated and open items are visited frequently for an outcome.

Documents added or uploaded to TMF/eTMF in a timeframe to ensure inspection readiness at all times.

Along with Communication, documentation is the key for the success of any project, remember if its **not** documented then it didn't happen or wasn't discussed.

Stay in touch with regulatory hot topics, an example in DM at the moment is 'Access to data'. You absolutely can't enter data into an eCRF if you are not the site, so avoid things like entering PDs into the eCRF. Ensuring no one can influence the data except the site, so no bulk changes, ensuring site has access to the data after the study – data cd, and that the study can be accessed in the

event of a later audit.


Thank You
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