

Building Quality into Clinical Development

- Outsourcing -
CRO point of view

CTTI Workshop on Quality Risk Management
Making Clinical Trials Fit for Purpose

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Clinical Trials: most affected areas for quality improvements

✓ Clinical

- Protocol design and adherence
- Subject recruitment, information and consent process
- Site selection and training / familiarization with the trial requirements
- Safety management and reporting
- Clinical operations, monitoring and documentation / records

✓ Records and Data Management

- Amount of documentation
- Data base set-up and CRF design
- Data validation and query management
- Technology

Areas of most common audit/inspection findings

- Protocol compliance
- Adequate and accurate records
- Informed Consent
- Adverse Event reporting
- Handling and accounting of IP

✓ Logistics

- IP shipment, handling and accounting
- Interaction with third parties (e.g. lab, imaging etc.)

Global mega study - Risk based monitoring concept

✓ Extend and nature of monitoring

- Pts visits every 3 months
- Monitoring intervals based on number of pts in site
(monthly >75 pts in site - 6 monthly <25 pts)
- All sites are monitored, all pts get limited SDV
(all pts get SDV for ICF, demographics, primary endpoints, related AEs and all SAEs)
- Some pts get 100% SDV
(randomly selected by the sponsor)
- Set of an “risk-assessment” level per site by CRA
(based on data and monitoring “findings”)
- CRA can also increase SDV level for a site
(based on “suspicion/gut feeling”)
- System performs also “risk-assessment” for sites automatically
(based on e.g. query rate, completion time for eCRFs...)

Global mega study - Risk based monitoring concept *Weaknesses*

- ✓ Chosen risk based monitoring model is inflexible
 - Sites think they can predict which pts are going to have 100%SDV
 - CRAs can keep own “risk-assessment” level low
by correcting findings directly at sites without reporting them (low SDV level)
 - A lot of additional forms and manuals overload CRA work
 - MVR content is required to be short and limited, format is fix
(→ re-training for CRAs – to report less and in a trial specific format)
 - Assuming that sites will “transfer” learning from “SDV-pts” to other pts
 - High re-training needs for investigators and site personnel
(e.g. calculation of compliance, reporting only “related” AEs vs. all AEs in the eCRF, correct reporting of study relevant exams and endpoints)

Global mega study - Risk based monitoring concept

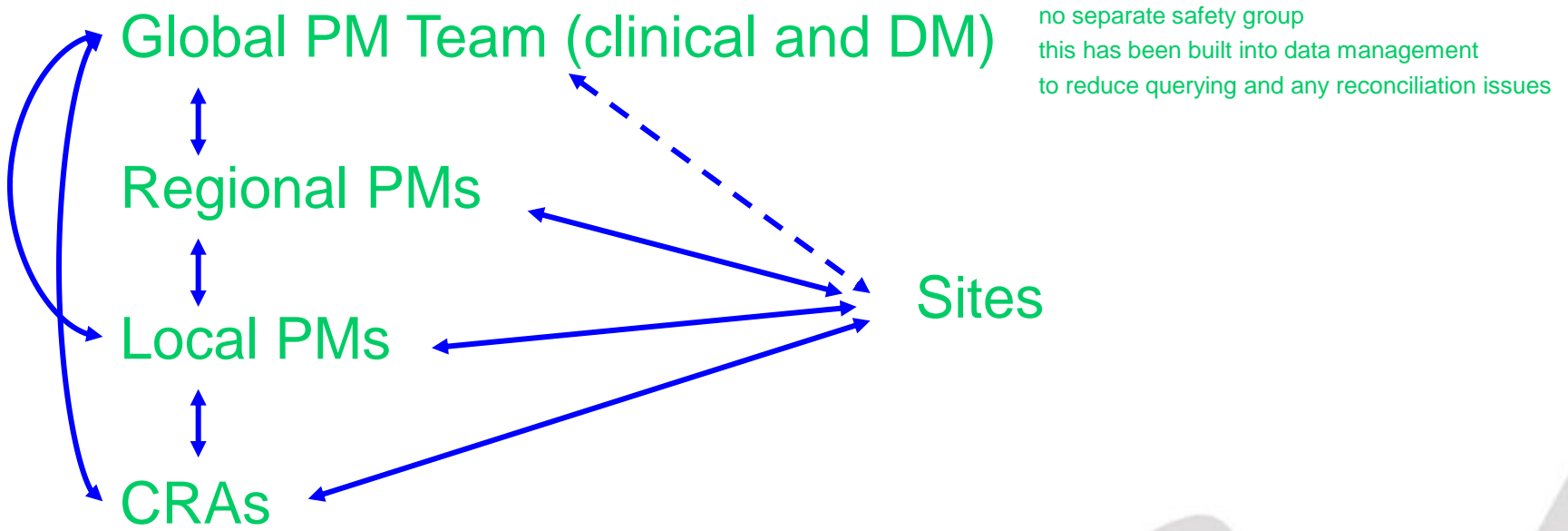
Weaknesses

✓ Interaction with data management

- “Risk-assessment” analyzed by system is not continuously received back by CRAs
- Information systems used are isolated and unconnected: eCRF, SDV tool, CTMS, IVRS
 - Complicated for CRAs
(not supporting their main tasks and responsibilities to an optimum)
 - Similar but different Logins/Passwords
 - Not easy to get/maintain an overview per site and patient

Global mega study - Risk based monitoring concept
Weaknesses

✓ Fragmentation of roles / distribution of tasks



- Lot of communication, TCs, e-mails
- CRAs perceive sponsor sometimes as “hyper-active”
 - *“too much time for communication and information exchange, too less time for work”*
 - the sponsor sees it as reacting to the risks shown in the risk assessments

Global mega study - Risk based monitoring concept

Chances for improvement

✓ Selecting individual visits for targeted SDV

- Can be triggered by and targeted to primary study endpoints
 - saves CRA's time for more/other important tasks on-site
- Provides good estimate on data quality over all pts
- Less "predictable"
 - forces Inv and CRAs to focus on all pts in the same way



Global mega study - Risk based monitoring concept

Chances for improvement

- ✓ Specific data management reports tailored for CRAs
 - Data quality
 - (e.g. query rate, reporting time, resolution time, protocol deviations, AE/SAE listing, lists of con.meds / con.diseases, outlier reports)
 - Listings on site and CRA performance
 - (e.g. KPIs of individual CRAs and their sites in comparison to regional and global average data)
- ✓ Data management-, safety reports and global oversight should be used to feedback CRAs for “adaptive” monitoring methods
 - Prioritize MON-Visits where the CRA is needed most
 - Data evidence based
 - Contrarily to fixed monitoring schedule accd. to monitoring plan
 - Content / tasks during the monitoring should be kept flexible
 - accd. to feedback from data management -, safety - and PM departments or other stakeholders and information

Rescue Data management within a biotech study

- ✓ Global Project - Sponsor outsourced to various vendors
 - Data Management was a different CRO than the Monitoring CRO
 - Sponsor had limited experience in data management and CRF design
 - Bad eCRF design
 - record flow on e-CRF pages was not top→down; left→right
 - language used was not short and simple
 - units pre-set (not matching every sites used units)
 - Lot of derived data (e.g. BMI instead of height and weight) without recording source data
 - eCRF page order did not match/support daily medical practice

Rescue Data management within a biotech study

✓ All of this resulted in:

- Programming of data validation rules required special caution
 - to create queries that were understandable for sites
- Data management had additional work
 - because of poor monitoring quality
 - monitors did not understand the eCRF well
 - Monitors did not support the sites adequately
- Sponsor had no DMP
 - change in data cleaning process from very detailed at the beginning to roughly data validation towards the end of the trial
- High data management costs
 - additional resources for data cleaning needed to keep timeline for db closure

Outsourcing strategy of a biotechnology company

- ✓ Limited resources (personnel, systems and money)
- ✓ Risk minimization was the goal
 - 5 clinical trials, each of them with 20 different vendors
 - Handling of 100+ vendors
 - Resource intensive vendor selection, oversight, audits
 - Communication has to go over sponsor's desk
 - SOPs management
(sponsor want to collect, review and approve all used SOPs from all vendors and trials)
 - Different data formats and locations
(all outsourced – no own database or system)
 - Overview on safety & efficacy of the product is nearly impossible
(no ISS or ISE, safety DB is outsourced to a vendor)



Protocol design and adherence

- ✓ Often comes from the sponsor
 - From HQs outside the territories where the study should be conducted
 - Designed to meet
 - Regulators expectations
 - Most current scientific knowledge and state-of-the-Art practice
 - Generate a positive result
 - Does often not meet
 - Patients expectations and needs
 - Often disable them to comply with the study schedule and requirements
 - Day-to-day medical practice
 - Easy reading and comprehension



Globalization

- ✓ High international study teams, let by sponsor
 - Different stakeholders
 - different agenda, motivation and risk
- ✓ Communication and information
 - flow is often inadequate and does not fit for all
 - e.g. technology, language, time zone, content and format
- ✓ Reporting an increased risk or bringing a new risk up is often perceived by the individuals as “*reporting own failure*”
- ✓ Team communication is often “status reporting” rather than exchange of experience and improvement targeted
- ✓ Team fluctuation results in lost of information (at all parties)

Quality by Design – where can quality planned in a trial?

1. Protocol
2. CRF
3. Subject Information and Consent Form
4. Communication Plan and Information Flow Chart / Team training
5. Data / Information exchange and communication (technical solutions)
6. Project Plan
7. Trial Master Filing Plan
8. Monitoring Plan
9. Data Surveillance Plan / Safety Monitoring Plan
10. AE / SAE / SUSAR reporting manual, forms and instructions
11. Data Management Plan
12. Statistical Analysis Plan
13. Auditing Plan

*Different approaches
Different level of detail*



892 patients

90 sites

22 countries

189 boxes

6 binder / box

500 pages / binder

567.000 pages

Quality by Design – where can quality planned in?

- ✓ Quality Management Plan
 - For individual studies
 - For the entire product development life cycle
- ✓ Measures and evidence from data should be preferred
 - as trigger for appropriate actions and adaptations during trial execution
- ✓ Caution with the human factor re. “whistle blowing”
 - especially when it comes to processes or systems



*“...where to spend the **right amount** of resources, time and money to achieve an **adequate level** of quality?”*

*The Answer requires
educated decisions*

THANK YOU

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