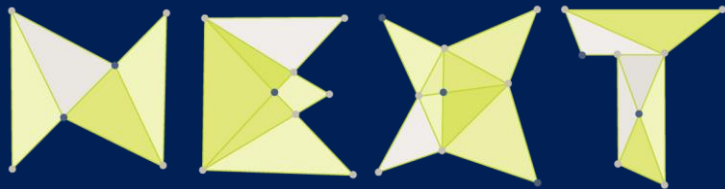
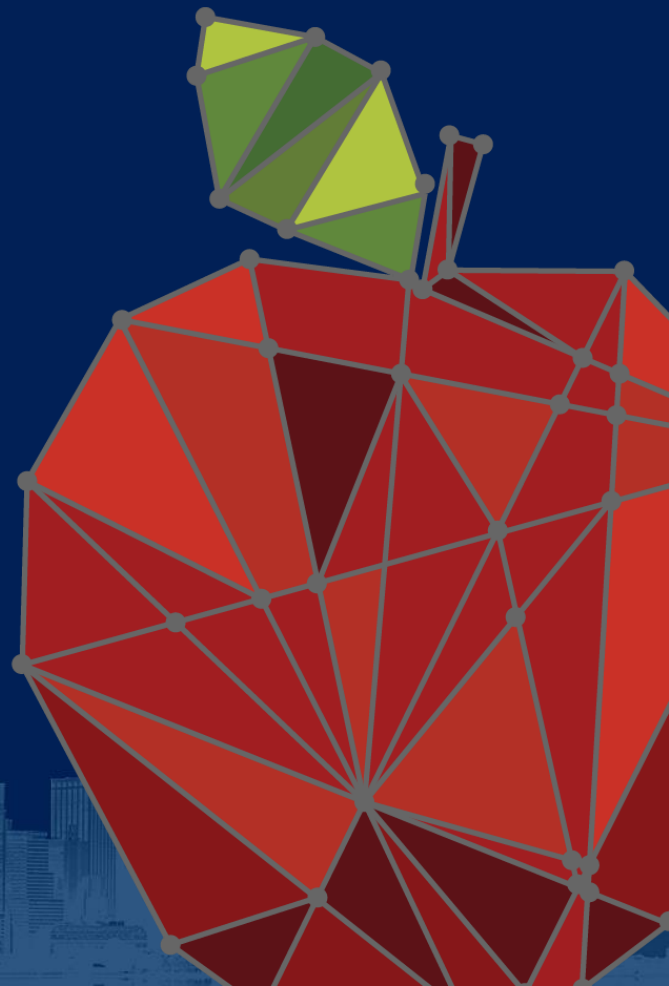


medidata



WHERE SCIENCE
MEETS TECHNOLOGY
MEETS THE FUTURE





PROMETRIKA

A FULL-SERVICE CRO

Innovative Clinical Development Solutions

The Era of Flexible Monitoring Models:

Centralized Real-Time Data Review and Utilization of
Targeted Source Document Verification

Heather Paden, Head of Clinical Operations

- Local regulatory knowledge, strong relationships with investigational sites and medical experts, and highly experienced cross-functional teams, worldwide.
- World-class data science powered by cutting-edge technologies, expert biostatistical analyses, and experienced regulatory medical writing.

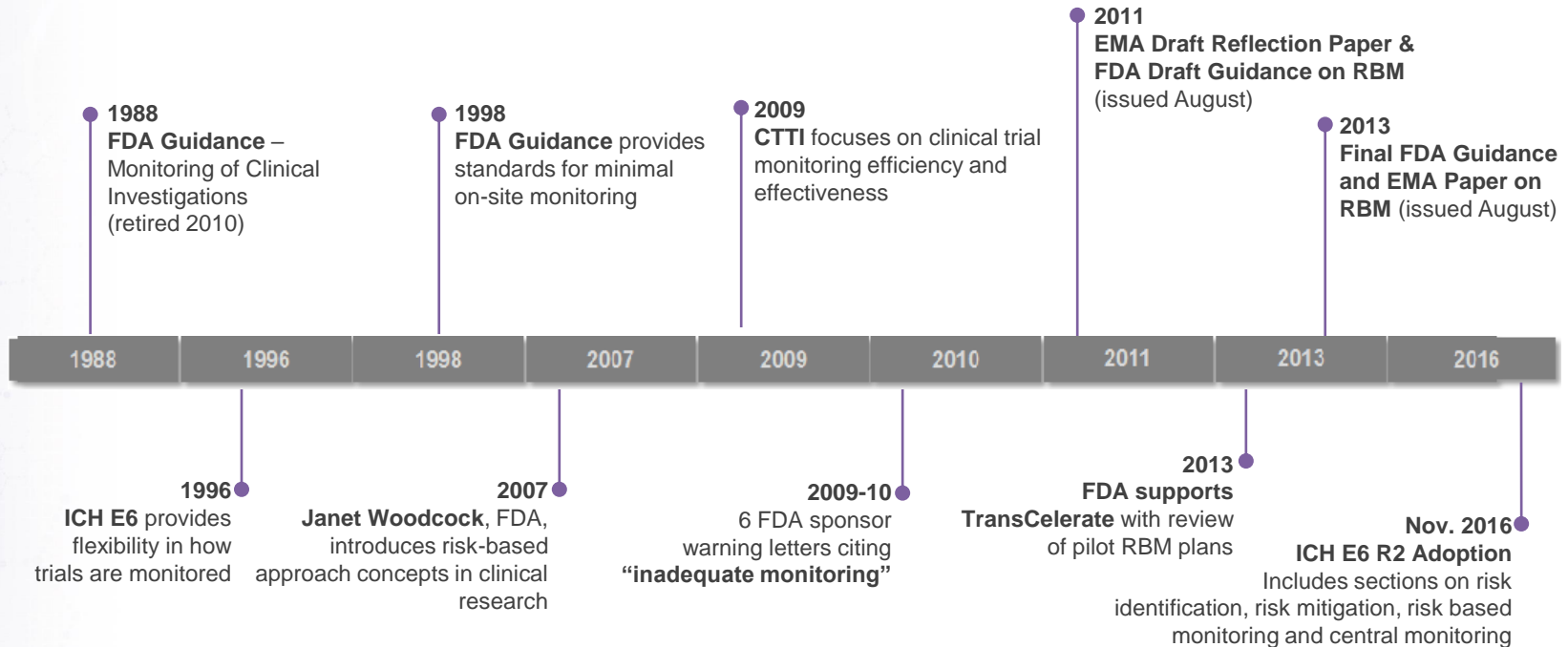
What's required?

Overview





- A change in mindset
- Rationale for different approaches to monitoring data
- Pre-requisites and tools
- Case Study: Value proposition in rare disease studies
- Considerations

A Change in Mindset

Regulatory Agencies Acknowledge Flexibility



The Evolution of Risk Based Monitoring

CTTI	FDA Guidance	EMA Reflections Paper	TransCelerate Paper
<p>Quality by Design</p> <ul style="list-style-type: none"> • Tailor monitoring approach • Protocol quality impacts monitoring quality 	<p>Quality Clinical Trial Data</p> <ul style="list-style-type: none"> • Assess Risk • Combination of monitoring activities • Tailor Monitoring Plan 	<p>Risk Based Quality Management</p> <ul style="list-style-type: none"> • Plan • Adapt • Build on experience and advances 	<p>RBM Methodology</p> <ul style="list-style-type: none"> • Holistic, proactive approach; risk assessment, mixture of remote & on-site monitoring 

Source: TransCelerate

ICH E6 Good Clinical Practices (R2)

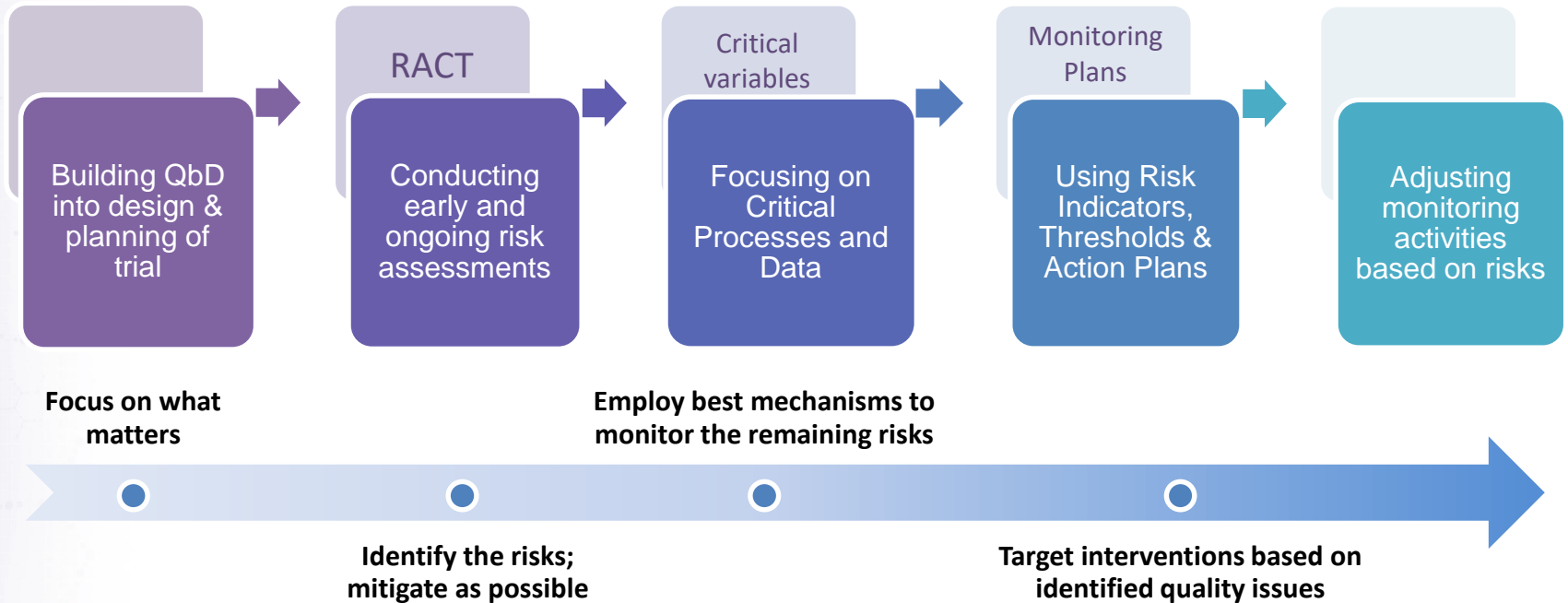
- Since original allowed flexibility in monitoring approaches
- Increased focus on Critical Data and Processes (trial activities essential to ensuring subject protection and reliability of trial results)
- Implement a system to manage quality
- Risk identification, risk evaluation, risk communication, risk control, risk review and risk reporting
- Monitoring based on Risk including the use of centralized monitoring to compliment or reduce on-site monitoring



Risk-Based Monitoring Methodology

- Risk Based Monitoring is more than just onsite monitoring, it is an end to end approach based upon Risk Assessments and Quality by Design
- TransCelerate has created an approach that has been adopted (and adapted) by big Pharma, CROs, etc.
- It has also given the software providers such as Medidata a roadmap to develop new tools to support the methodology

Risk-Based Monitoring Methodology



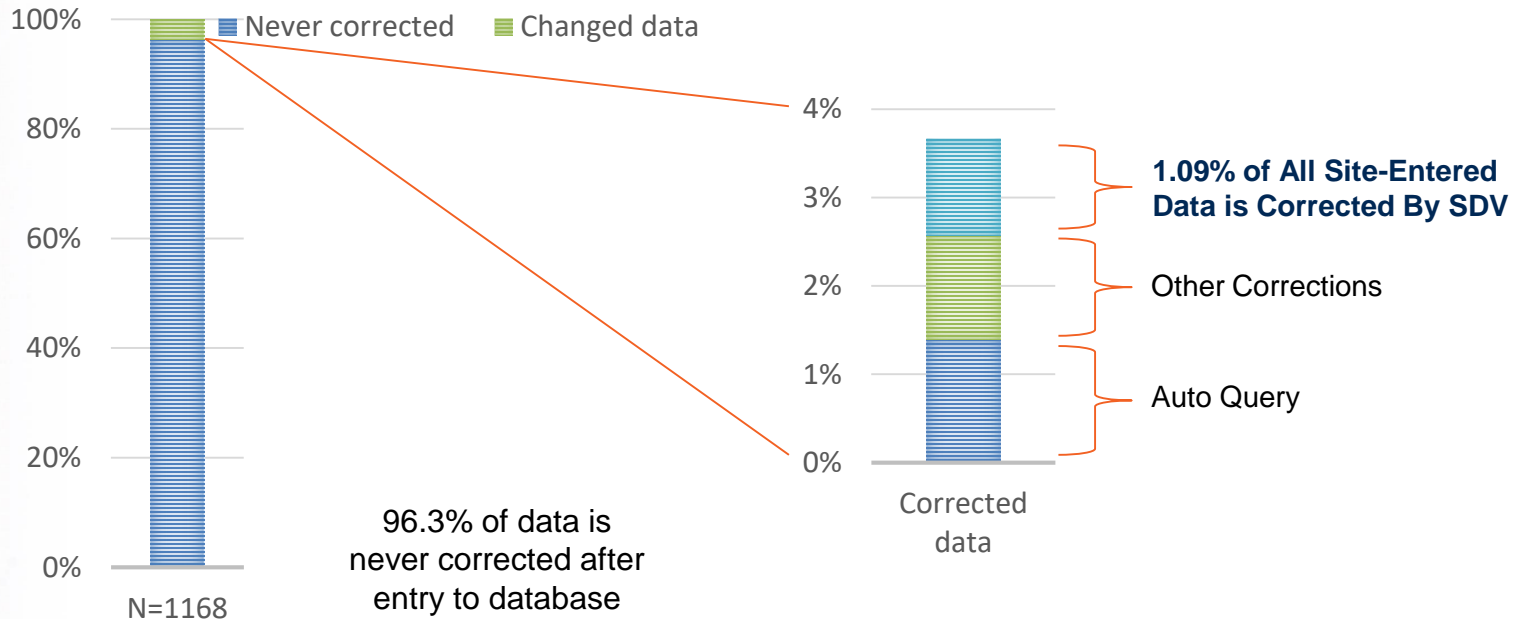
Rationale for Different Approaches to Monitoring Data

One Size Does Not Fit All

- Not all studies are the same, similarly not all sites are the same....
....so why monitor them in the same way?
- The traditional 100% Source Data Review (SDV) approach has been shown in studies to have little impact on overall data quality but is time consuming for CRAs
- Programmatic assisted monitoring centrally is faster, cheaper and more effective at monitoring data
- Free up CRA time on-site to perform higher value tasks that cannot be assessed directly from the data

Retrospective SDV Analysis*: Additional Insight into Metric #2

Impact of SDV on Site-Entered Data



* Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials: Therapeutic Innovation & Regulatory Science 2014, Vol. 48(6) 671-680

Pre-Requisites & Tools

Pre-Requisites

- An organization willing to change!
- Successful TSDV relies on proper risk identification
- A solid foundation based upon risk and understanding what data/processes are important
- Agreement on which monitoring strategies are best suited to ensure quality and data integrity
- Centralized monitoring is reliant upon timely access to data
- Tools to support
 - The assignment and tracking of onsite monitoring
 - Centralized monitoring (from programmed edit checks, monitoring listings and tables...to advance statistical machine learning tools)

Targeted SDV (TSDV)

- TSDV is a tool that allows for an advanced method to assign and track SDV
- Through the use of Blocks and Tiers advanced assignments can be made
 - e.g. the first subject at each site could be 75% SDV, followed by 25% for each subsequent subject
- Changes at study, region, individual sites or individual subjects can be made

Case Study



TSDV Subject Management

- Subject Override
- Subject Retrospective
- Subject Include

Mediclin-X (OTHER) Subject Override

Subjects: [Search](#) [Clear](#)

Select Site Group:

Select Site:

Batch Mode Run Retrospective Backfill Open Slots Show SiteGroup and Sites Only Show Subjects In Inactive Plan(s) [Export](#)

Subject	Original Tier	Current Tier
10421122	All Forms (Default Tier)	All Forms (Default Tier)
10421123	Incl/Excl/Demog (Custom Tier)	Incl/Excl/Demog (Custom Tier)
10421124	Critical Data (Custom Tier)	Critical Data (Custom Tier)
10421125	Incl/Excl/Demog (Custom Tier)	Incl/Excl/Demog (Custom Tier)
10421126	Critical Data (Custom Tier)	Critical Data (Custom Tier)
10421127	Incl/Excl/Demog (Custom Tier)	Incl/Excl/Demog (Custom Tier)
10421128	All Forms (Default Tier)	All Forms (Default Tier)

Page: [1](#) [2](#) [3](#) [4](#) [5](#) [6](#) [7](#)

[Subject Override](#) [Cancel](#)

Subject TSDV Tier assignment.

Subjects 10421127 and 10421128 assigned to different tiers.

Case Study: Value Proposition in Rare Disease Studies

Case Study

Study Design:

- Phase 2, Open-Label
- Three times a week dosing of ABC-123456 in subjects with a transfusion dependent rare blood disorder
- Local and central labs
- MRI derived key secondary endpoint
- Duration: 12 months

Which terms above that reflect potential Critical Data and/or Critical Processes?

Case Study

10421127
Adverse Events

Freeze All Fields Inactivate Page ⚙

Adverse Events, Log Lines

Back To Complete View < Previous Line Line 1 of 1 Next Line >

Adverse Event: ⓘ	MIGRAINE HEADACHE
Start Date (DD MON YYYY): ⓘ	18 OCT 2018
Stop Date (DD MON YYYY): ⓘ	
Ongoing/Continuing: ⓘ	Yes
Relationship to Investigational Product: ⓘ	POSSIBLY RELATED
Action Taken (Investigational Product): ⓘ	None Returned

10421128
Adverse Events
Requires Verification

Adverse Events, Log Lines

Back To Complete View < Previous Line Line 1 of 1 Next Line >

Adverse Event: ⓘ	MIGRAINE HEADACHE	<input type="radio"/> Verify
Start Date (DD MON YYYY): ⓘ	17 OCT 2018	<input type="radio"/> Verify
Stop Date (DD MON YYYY): ⓘ	17 OCT 2018	<input type="radio"/> Verify
Ongoing/Continuing: ⓘ	No	<input type="radio"/> Verify
Relationship to Investigational Product: ⓘ	POSSIBLY RELATED	<input type="radio"/> Verify
Action Taken (Investigational Product): ⓘ	Drug Interrupted	<input type="radio"/> Verify

AE forms of the 2 subjects with almost identical data.
10421128 requires all fields be verified while the other does not.

Case Study

Filters Clear Filter

Subject 10421127 ✕ 10421128 ✕

Update Results

Select All	Subject ▲	Subject Status	Folder	Form
<input checked="" type="checkbox"/>	10421127	Randomized	Screening	Demographics
<input checked="" type="checkbox"/>	10421127	Randomized	Screening	Inclusion / Exclusion Criteria
<input checked="" type="checkbox"/>	10421127	Randomized	Screening	Visit Date
<input type="checkbox"/>	10421128	Randomized	Screening	Demographics
<input type="checkbox"/>	10421128	Randomized	Screening	Inclusion / Exclusion Criteria
<input type="checkbox"/>	10421128	Randomized	Screening	Serum Cholest
<input type="checkbox"/>	10421128	Randomized	Screening	Visit Date
<input type="checkbox"/>	10421128	Randomized	Screening	Randomization
<input type="checkbox"/>	10421128	Randomized	No Folder	Adverse Events
<input type="checkbox"/>	10421128	Randomized	Visit 1	Dispensation

11 Total Result(s) Per page 10 25 50 100

Set Verified

As you can see, only 3 forms requiring verification for 10421127 and multiple others for 10421128 even though they have virtually identical data entry.

Considerations

Considerations

- CRA visits – saving an hour on SDV, what does it actually mean?
- Centralized monitoring relies upon near real-time access to data to be most effective
- All monitoring needs to be documented, including centralized monitoring

ANY
QUESTIONS

