Risk Based Monitoring - a case study

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Objectives and Challenges

The Veloxis Background and Objective

- Veloxis has
  - Included risk assessment as a central tool to all projects since before 2007.
  - Worked with reduced SDV and targeted monitoring through CROs since 2008.
  - Used Key Performance Indicators (KPIs) to track delivery (cost, progress and quality) and bonus/penalty clauses to enforce it.

- We wanted to take the next step into RBM!

Challenges to Implement RBM

- Veloxis has 3 employees in clinical operations and 1 employee in clinical supplies (3 ongoing studies).
- No other supporting departments.
- Current eCRF provider does not support RBM.
- Need to pull as much work in house as possible to cut costs.

To Overcome the Challenges

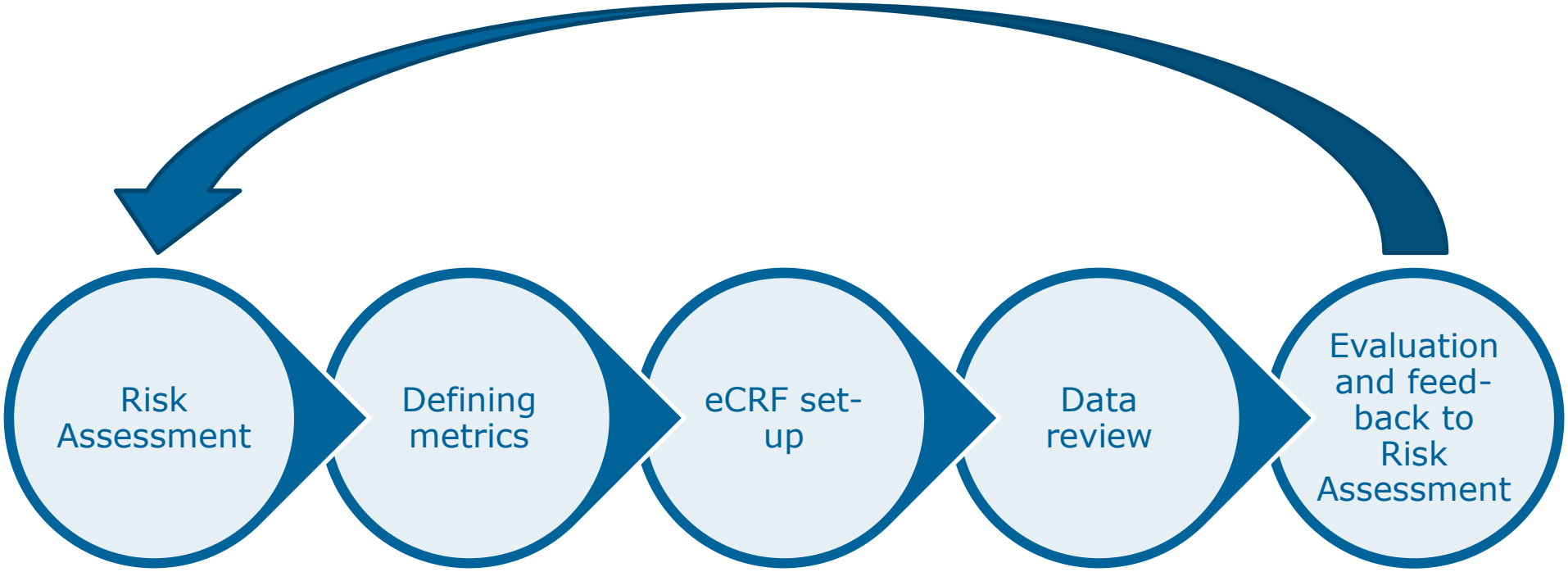
- We needed to
  - Select a new eCRF provider with some RBM capabilities.
  - Perform most of the study procedures in house.
  - Choose the correct study without too many challenges or resource needs.

The Chosen Set-Up

- eCRF
  - 5 venders approached and TrialMaster provided by OmniComm selected.
- Split of responsibilities
  - Pharmacovigilance and statistical support was outsourced.
- Case Study
  - A phase 3B single center PK study in 32 patients in the USA.
  - The planned duration was 2 months.

Implementing and Executing the Risk Based Strategy

Process Flow



Risk Assessment

- A risk assessment was performed by clinical operations with input from
  - Medical Monitor
  - Medical Affairs
  - Data Management
  - Quality Assurance
  - Bio-Statistician

- All risks were assessed and assigned a risk rank.

Translating Risk Rank Into SDV

- Each risk that pertained to data entry was evaluated for level of review based on rank

ID	Risk description / Failure mode	Consequence / Effect	What could cause the failure	Prob.	Cons.	Risk Value	Risk Owner
1	Missing endpoints	Invalid conclusion of the study endpoint	Patients lost to follow up Missing PK data or incorrect dosing within 48 hours of PK visit	3	5	15	cvs
2	Violation of in/exclusion criteria	wrong patient population safety issue	inadequate screening or knowledge of patient history inadequate training of site staff resource issues list most important in/exclusion criteria	2	5	10	cvs
6	Missing or late safety reporting	missing or late safety reporting can lead to regulatory complications	lack of knowledge at site or by patients	3	5	15	cvs
5	Site performance issues	non-recruiting sites will consume resources that are better used elsewhere bad performance is a risk for the study in general	inadequate site resources improper instructions/training wrong match of site and study	2	3	6	cvs

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Defining Metrics

- 100% SDV for 5 patients (or 5%); first two + randomly selected patients
- SDV of the first SAE at each site
- SDV all critical variables for 10% of the patients
  - eligibility (incl. ICF) and randomization
  - Patient disposition and major endpoints (PK and exposure)
  - major deviations
- Review all critical variables for all patients (as above)
- Review important data points for 10% of the patients
  - Demographics
  - all AEs
  - Pharmacogenomics
  - Deviations

Set-up of TrialMaster

- TrialMaster has two parameters to control your RBM set-up
  - The monitoring level determines how much data will be marked for SDV for a given patient.
  - The site rating determines the distribution of patients between the monitoring levels at a site.

Site Rating	Low Trust	Medium Trust	High Trust
All Forms	A%	X%	C%
Critical Forms	B%	Y%	V%
None	C%	Z%	S%
Total	100%	100%	100%

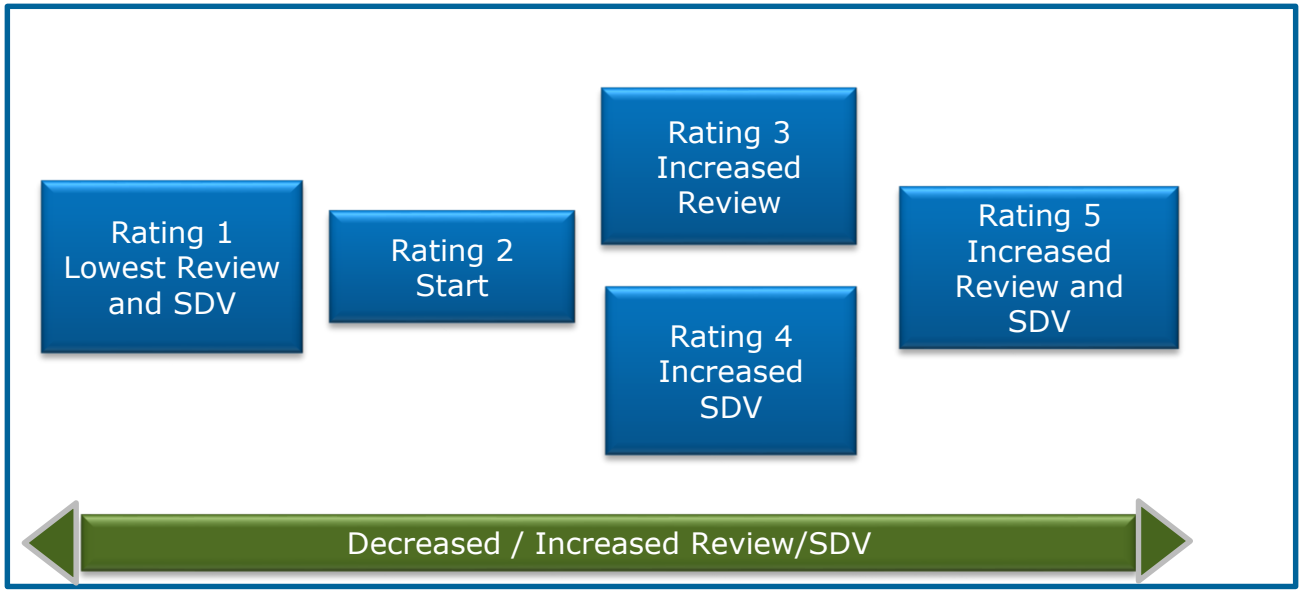
Set-up of TrialMaster (cont.)

Default site rating

Site Rating	1 Decreased SDV	2 Normal	3 Increased Review	4 Increased SDV	5 Increased Review and SDV
All Forms SDV	2 first patients and then 10%	2 first patients and then 10%	2 first patients and then 10%	2 first patients and then 10%	2 first patients and then 20%
SDV critical	0%	10%	10%	30%	40%
Review important	10%	10%	30%	10%	40%
None	80%	70%	50%	50%	0%
Total	100%	100%	100%	100%	100%

The review of critical data points for all patients happened via reports generated by TrialMaster and was not included in the matrix above.

Adjusting Site Rating



- The site rating can be modified according to site performance

Review of data

- No edit checks or automated queries were programmed.
- Reports were used to review large amount of data at a glance instead of clicking through the eCRF.
  - All dates and time points of the screening visit to ensure that all procedures were done after informed consent was obtained.

Eligibility at a Glance

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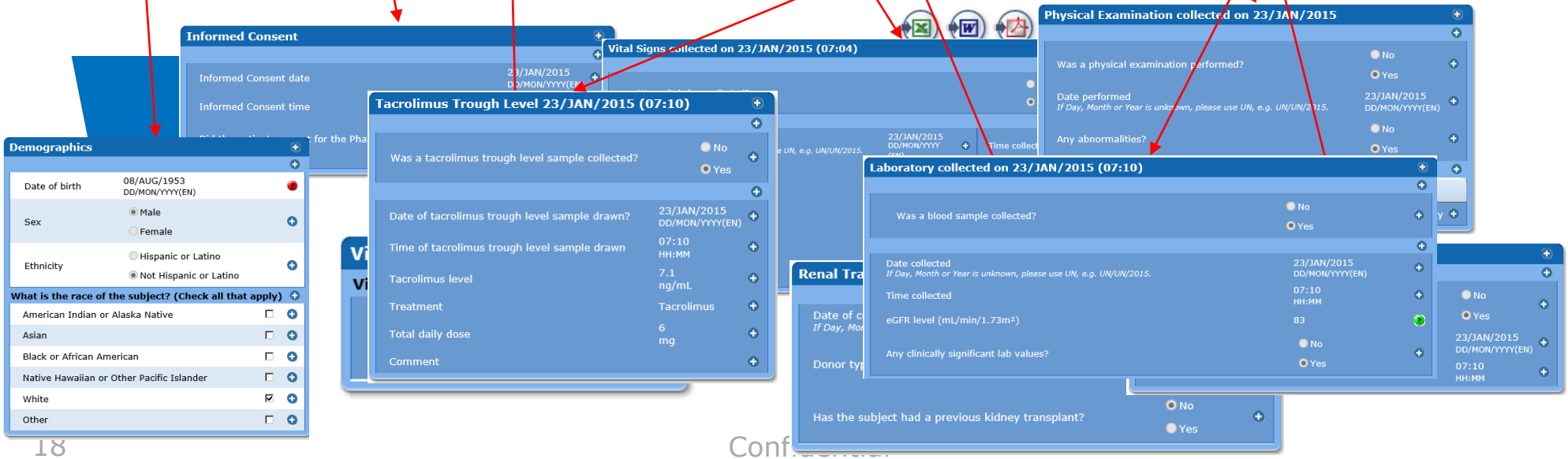
Pt. #	DOB	Age	Gender	ICF Date	ICF Time	Visit #	Visit Date	VS Done	VS Date	VS Time	Tx Date	years transpl.	PE Done	PE Date	PE Abn	PCG Done	PCG Date	PCG Time	Lab Done	Lab Date	Lab Time	Lab Abn	Trough Done	Trou
001	08-aug-19[illegible]3	62	M[illegible]e	23-jan-2015	06:59	V1	23-jan-2015	Yes	23-jan-2015	07:04	09-nov-20[illegible]0	5	Ye[illegible]s	23-jan-2015	**Yes**	Yes	23-jan-2015	07:10	Yes	23-jan-2015	07:10	**Yes**	Yes	23-ja
002	17-feb-1955	[illegible]	Female	23-jan-2015	07:07	V1	23-jan-2015	Yes	23-jan-2015	07:11	04-okt-2007	8	Yes	23-jan-2015	**Yes**	Yes	23-jan-2015	07:17	Yes	23-jan-2015	07:17	**Yes**	Yes	23-ja
003	10-dec-1961	54	Male	23-jan-2015	07:15	V1	23-jan-2015	Yes	23-jan-2015	07:19	08-jun-2006	9	Yes	23-jan-2015	**Yes**	Yes	23-jan-2015	07:25	Yes	23-jan-2015	07:25	No	Yes	23-ja
004	13-feb-1952	63	Male	23-jan-2015	07:22	V1	23-jan-2015	Yes	23-jan-2015	07:26	30-apr-2012	3	Yes	23-jan-2015	**Yes**	Yes	23-jan-2015	07:32	Yes	23-jan-2015	07:32	**Yes**	Yes	23-ja
004	13-feb-1952	63	Male	23-jan-2015	07:22	V1	23-jan-2015	Yes	23-jan-2015	07:26	30-apr-2012	3	Yes	23-jan-2015	**Yes**	Yes	23-jan-2015	07:32	Yes	23-jan-2015	07:32	**Yes**		27-ja
005	02-jan-1969	46	Male	23-jan-2015	07:30	V1	23-jan-2015	Yes	23-jan-2015	07:33	22-sep-2011	4	Yes	23-jan-2015	No	Yes	23-jan-2015	07:38	Yes	23-jan-2015	07:38	**Yes**	Yes	23-ja
006	05-jun-1982	33	Male	23-jan-2015	07:33	V1	23-jan-2015	Yes	23-jan-2015	07:47	24-aug-2010	5	Yes	23-jan-2015	No	Yes	23-jan-2015	07:50	Yes	23-jan-2015	07:50	**Yes**	Yes	23-ja
013	08-sep-1975	40	Female	23-jan-2015	08:49	V1	23-jan-2015	Yes	23-jan-2015	08:55	19-jul-2005	10	Yes	23-jan-2015	No	Yes	23-jan-2015	09:00	Yes	23-jan-2015	09:00	**Yes**	Yes	23-ja
014	19-nov-1980	35	Female	23-jan-2015	09:01	V1	23-jan-2015	Yes	23-jan-2015	09:08	09-sep-2006	9	Yes	23-jan-2015	No	Yes	23-jan-2015	09:15	Yes	23-jan-2015	09:15	**Yes**	Yes	23-ja
014	19-nov-1980	35	Female	23-jan-2015	09:01	V1	23-jan-2015	Yes	23-jan-2015	09:08	09-sep-2006	9	Yes	23-jan-2015	No	Yes	23-jan-2015	09:15	Yes	23-jan-2015	09:15	**Yes**		28-ja
015	18-jan-1968	47	Male	26-jan-2015	08:42	V1	26-jan-2015	Yes	26-jan-2015	08:45	19-jul-2011	4	Yes	26-jan-2015	No	Yes	26-jan-2015	08:53	Yes	26-jan-2015	08:53	**Yes**	Yes	26-ja
007	19-jul-1954	61	Male	23-jan-2015	07:55	V1	23-jan-2015	Yes	23-jan-2015	08:00	18-jan-2011	4	Yes	23-jan-2015	**Yes**	Yes	23-jan-2015	08:11	Yes	23-jan-2015	08:11	**Yes**	Yes	23-ja
008	27-jan-1954	61	Male	23-jan-2015	07:38	V1	23-jan-2015	Yes	23-jan-2015	07:40	10-nov-2005	10	Yes	23-jan-2015	No	Yes	23-jan-2015	07:45	Yes	23-jan-2015	07:45	**Yes**	Yes	23-ja
009	09-okt-1982	33	Male	23-jan-2015	07:54	V1	23-jan-2015	Yes	23-jan-2015	08:00	28-maj-2009	6	Yes	23-jan-2015	No	Yes	23-jan-2015	08:30	Yes	23-jan-2015	08:30	No	Yes	23-ja
010	02-sep-1985	30	Male	23-jan-2015	08:33	V1	23-jan-2015	Yes	23-jan-2015	08:44	02-okt-2008	7	Yes	23-jan-2015	No	Yes	23-jan-2015	08:43	Yes	23-jan-2015	08:43	**Yes**	Yes	23-ja



Study Oversight and Risk Updates

- A study oversight plan was created describing data cleaning/handling, monitoring and metrics collection.
- Monthly reviews were performed collecting data from the eCRF, monitoring, correspondence, vendors, status updates etc.
- A report was written with an overall status conclusion and recommendations on changes to the risk matrix and site rating.

When to Adjust Site Rating?

A mix of objective and subjective measures:

- Less than 5% errors in two consecutive months/tests => Better rating.
- More than 10% errors in one month/test => more intensive review.
- If a patient is special => change monitoring level of that patient.
- Input from monitoring, correspondence, deviations, outliers etc.

Observed Metrics
- still in progress

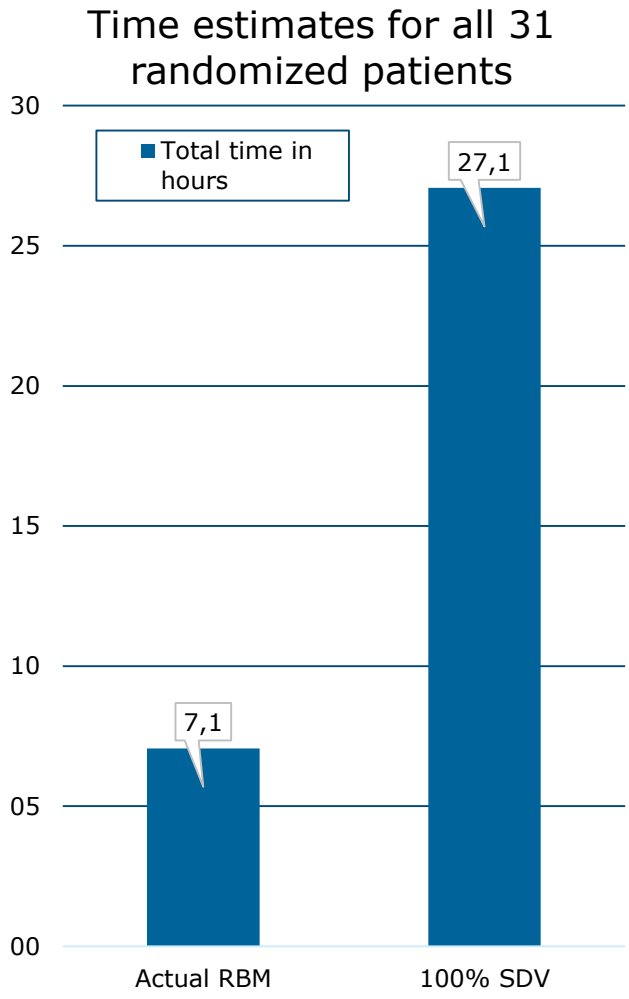
Extent of Data Review

- Within the RBM
  - Data have been reviewed with a few exceptions.
    - A few entries are still pending.
    - SDV is pending for 4 patients (2 for 100% SDV and 2 for SDV of critical data).
- Outside the RBM
  - All PK data have been SDV'ed (1736 data points)
  - SDV performed on two additional patients
  - SDV on all consent forms
  - Review of data for ~ 5 patients
- Statistical programming (=edit checks)

Actual and Estimated Time Spent

- Total time for each task was measured and normalized per patient.
- To estimate SDV time, mean time for 3 patients was used.

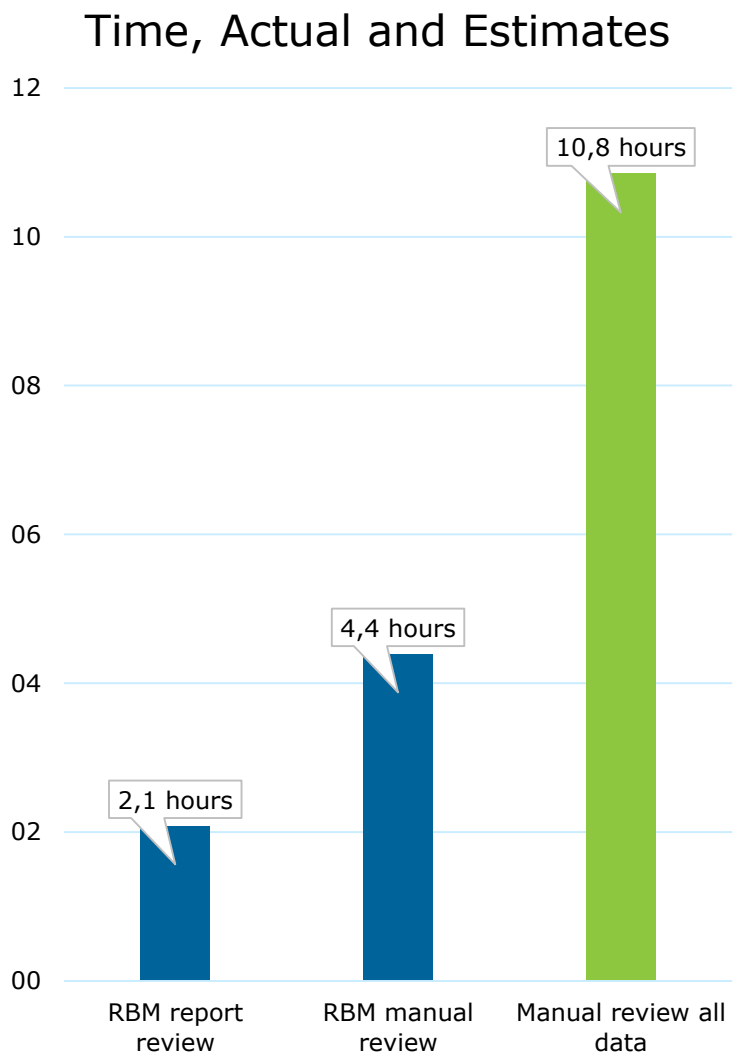
RBM item	n	RBM (min/pt)	Manual (min/pt)
Review critical data items	31	3,9	7,2
100% SDV	3	52,4	52,4
SDV of important data items	1	12,2	12,2
Review of important data items	3	1,5	13,8



Additional Observations

- The RBM review was performed according to plan.
- A manual review was performed of the same data points as in the reports for comparison.
- For reference a worst case was estimated if all patient data had to be manually reviewed

Method	Total time (hrs.)
RBM report review	2,1
RBM manual review	4,4
Manual review of all data (estimated)	10,8



…and the Quality

- A total of 70 observations were made
- 63 observations were made within the RBM
  - 4 could only be observed during SDV (e.g. wrong date of birth).
  - 18 were observed on the 11 sampled patients for 100% SDV, SDV of critical and review of important data points.
- 7 observations were made outside of RBM
  - 5 of these were caught during other review (payment, statistician etc.)
  - 2 would not have been caught?

Conclusion and Next study

Extrapolating the Errors We found?

- 11 patients were reviewed/SDV'ed; 18 observations
  - Chances are that there might be more errors.
- Our RBM set-up ensures that the errors we might have missed cannot change the outcome of the study – except one.
  - We missed one important point – SDV of PK time points – which was remedied.

- The overall risk to the study is therefore acceptable!

Where Did We Not Look?

- We have used data review which does not eliminate the risk of false positive entries…
- AE and con meds start/stop + consistency was not checked.
- Vital signs not checked.

- These are risks we are willing to accept for a PK study of 3 weeks participation.

Setting Up the Next Study

- Consider more thorough SDV for the primary endpoint(s).
- Set-up automated queries/edit checks.
- Keep the site ratings as is and use site specific data checks outside RBM if needed.
- Continue to utilize reports to review data.

- Consider how to compare site and/or CRA performance when more sites are used.
- For studies with a safety outcome, AEs might have a higher risk rank.
- Determine how audit observation will be used as part of the RBM strategy.

Was the Objective Met?

Objective:
We wanted to take the next step into RBM!

- YES! - We have completed one study according to our RBM approach:
  - Estimated data cleaning time was reduced by 50% 
  - 30% of the data review time was spent in-house 
  - Overall quality is acceptable 
  - No critical errors have been missed… 
  - No overall time saved 
  - 44% cost savings on CRO expenses 
  - 25% travel costs saved 

Recommendations

If You Have Not Used RBM Before

- Evaluate the size of the study and the efforts needed to set up RBM vs. normal procedure.
- Include the entire team in risk assessment.
- Use both objective and subjective measures (fairly) in the risk assessment.
- Define your SDV/review/no action data groups with care
- Utilize the eCRF to make automatic queries for dates and time ranges.
  - Set these edit checks right the first time!
- Build reports up front and follow data on an ongoing basis – educate sites on the go.

Try it!

Questions?