

Harmonizing SDTM at the Source: Designing Collection Instruments that Support Sponsor Standards

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Roadmap

- ▶ Introduction
- ▶ History/ 2017 Recap
- ▶ 2019 How did we do?
- ▶ SDTM automated delivery
- ▶ Challenges faced
 - Ongoing data challenges and SDTM delivery
 - Handling of local laboratory data
- ▶ What the future looks like
 - Xcellerate
 - Improved 3rd party data handling
- ▶ Conclusion



Introduction

- ▶ AZ Overall operational goal is to 'Get Closer to the Data'
 - Focus on best practice for Early Clinical Development (ECD)
- ▶ In 2017, AZ / Covance entered into a partnership agreement
 - Data Management / Analysis and Reporting (A&R)
 - Shared responsibility and accountability at all levels
 - Covance provides core DM and A&R tasks
 - AZ to perform adhoc tasks
 - AZ / Covance team members to 'sit alongside' on clinical study teams
- ▶ 2019 update on the progress we have made
- ▶ Highlight challenges and look to the future



Previous Model

- ▶ Standardized at the RAW to SDTM mapping level
- ▶ CRO provides SAS datasets compliant to RAW data standards
- ▶ CRO given flexibility to build at the EDC level
- ▶ Can lead to variation at the EDC level
- ▶ Focus away from the data collection end and investigator experience

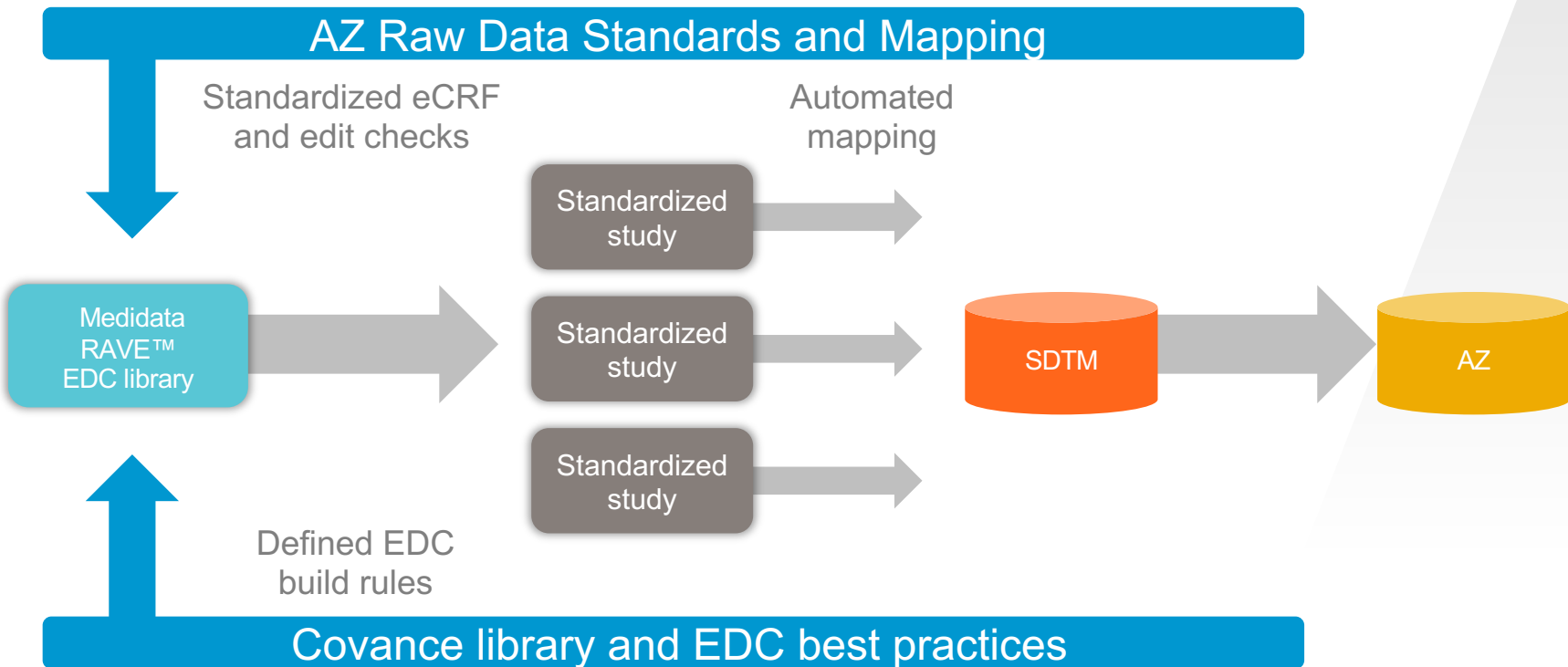


Proposed Goals 2017

- ▶ In order to meet the AZ operational goal 'Get closer to the Data', the following objectives were set:
 - Focus on EDC design and investigator experience, making the best use of technology
 - Automate mapping to SDTM where possible
 - Stay within the bounds of corporate AZ SDTM standards and processes
- ▶ Underpinned by the Partnership philosophy and a Joint Governance model



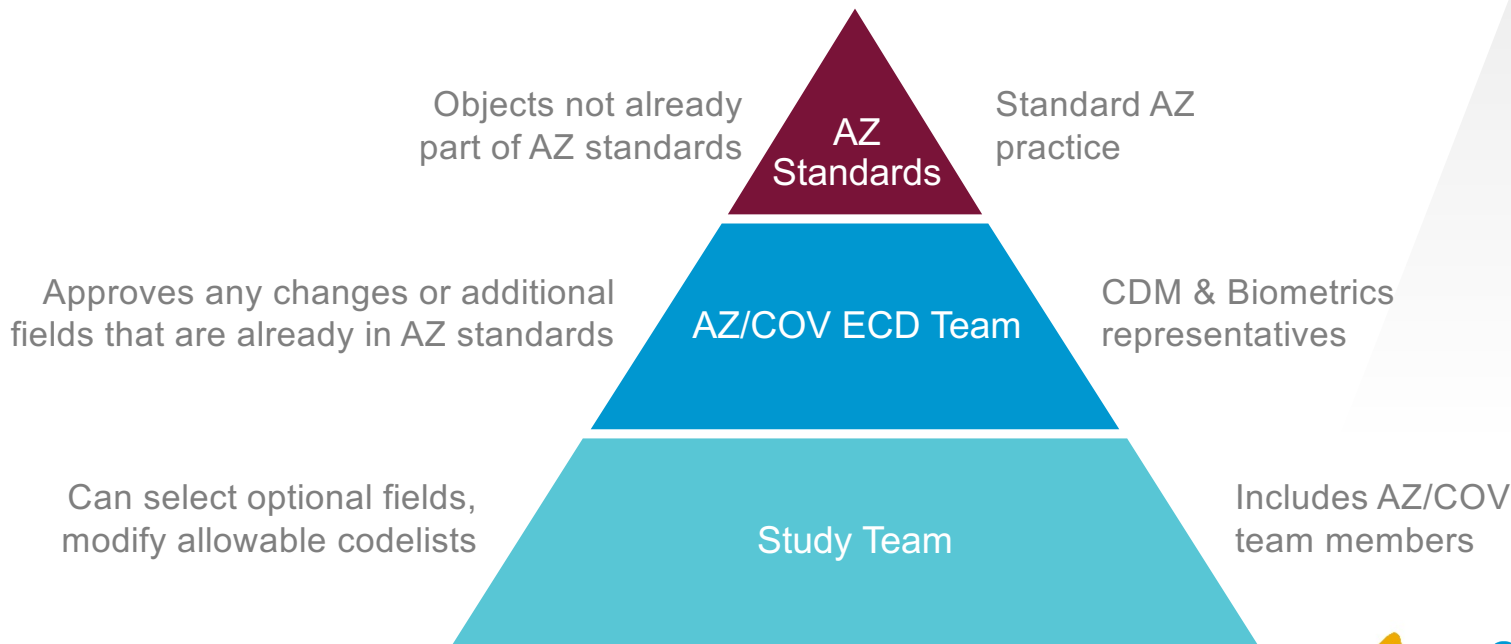
Proposed Model



Shared Standards Governance

Joint AZ / Covance (COV) Standards Governance Team established to manage ECD standards:

Regular meetings | Approve local level requests | Track AZ Standards requests



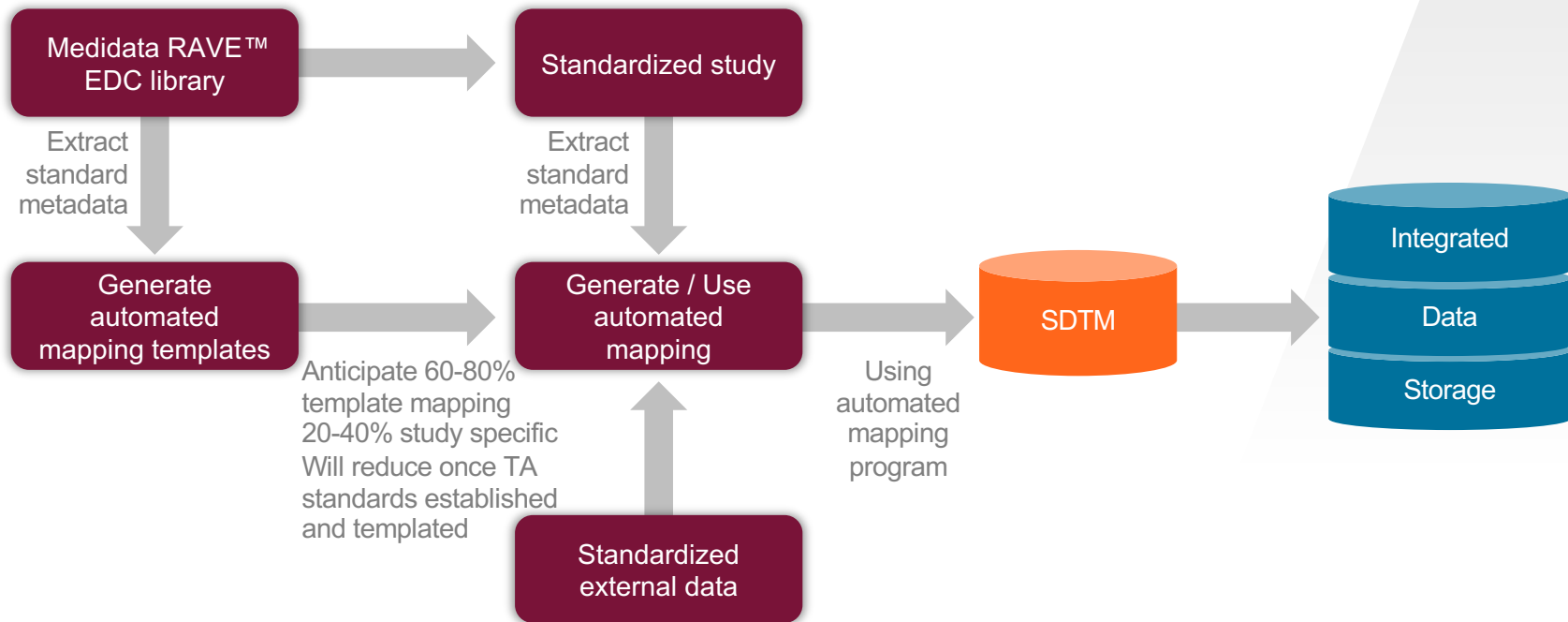
Scope of Standards Governance

- ▶ Broaden the scope of standards to include EDC standardisation, fully end-to-end:
 - EDC build rule definition
 - Visit naming / scheduling
 - Edit checks
 - EDC form visibility rules and dynamics
 - Integration definition
 - EDC reporting
- ▶ Development of tools to be used to assure compliance to standards.



Proposed Automated SDTM mapping plan

AZ Raw Data Standards and Mapping



Where we were in 2017

- ▶ Core set of Cross-TA standards agreed
 - 25 eCRFs defined
 - Edit check specifications drafted
 - Some derivations too
- ▶ Defined Visit structures – visit names, unscheduled visits
- ▶ EDC best practices defined
- ▶ Integrations defined and agreed
 - IVRS | Safety | CTMS
- ▶ Governance process defined
 - AZ/COV team established
 - Defined end to end standards approval process
- ▶ 5 studies live by the end of 2017.



2019 – How are we doing?

► Standards Status:

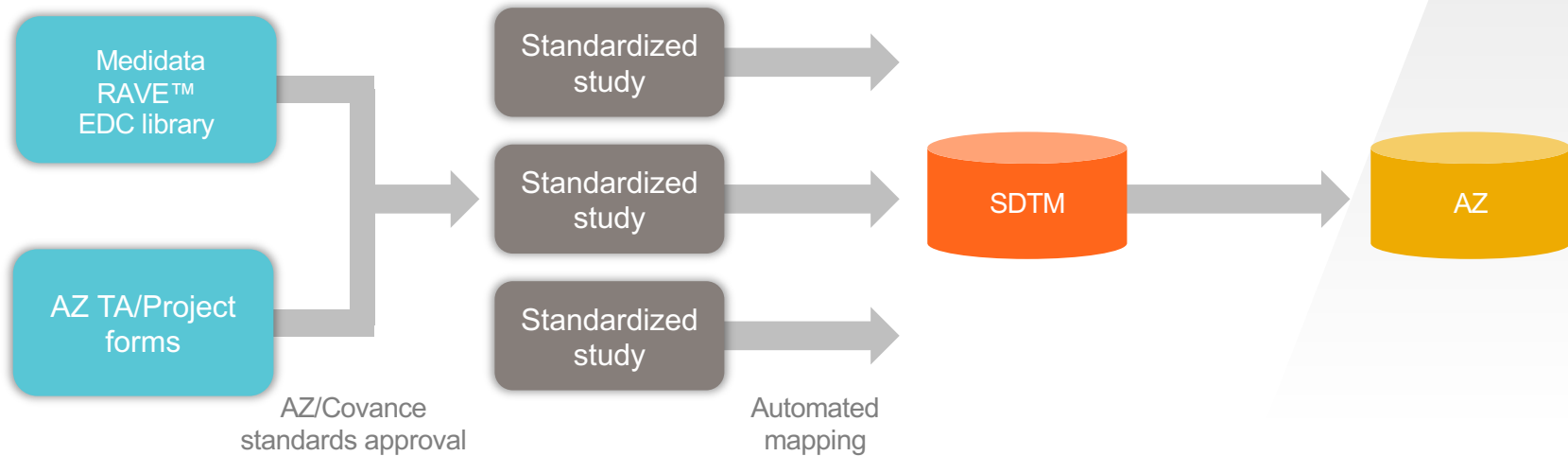
- Rave Global Library Volume version 2 published
- 47 Forms
- 1000 Edit Checks

► Study Status:

- 12 studies – Oncology heavy, including 2 platform studies
- 1 Study close out
- 3 Interims have been successfully delivered
- Numerous Data Cut Offs delivered
- + 100,000 SDTM datasets delivered



Current Build Model

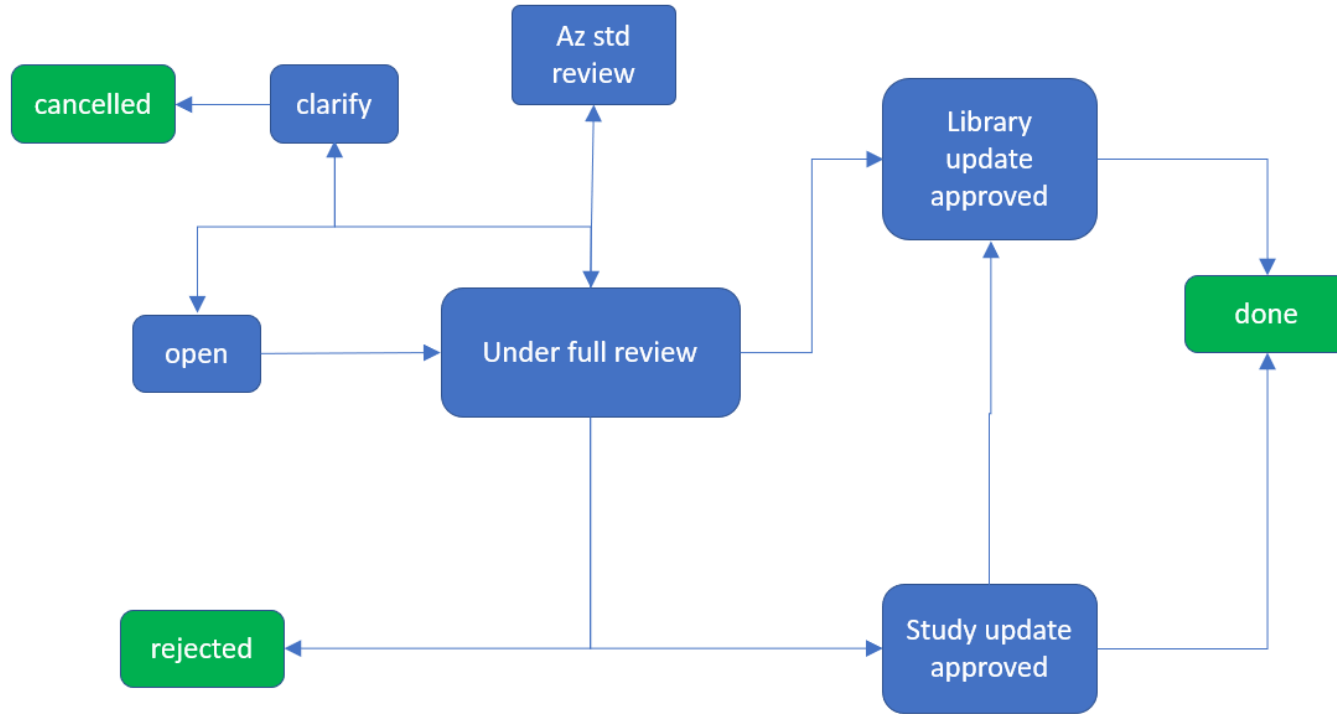


JIRA implementation

- ▶ Implemented a system to track requests to deviate from the standard eCRFs, use additional AZ TA/Study level forms
 - AZ and Covance staff have access
- ▶ Manage the updates and planned releases to the eCRF library
 - eCRF build team are able to easily see the list of pre-approved changes
 - Extended to include documentation updates and planned releases
- ▶ Considered including requests to deviate from AZ SDTM standards – onhold
 - TAT on AZ SDTM updates is long
 - Large number of study specific mappings



Typical JIRA® workflow



JIRA® DASHBOARD



JIRA

Your work

Dashboards

Projects

People

Issues and filters

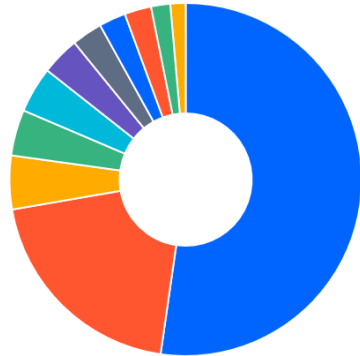
Jira settings

Dashboard

Introduction

Welcome to the SDO standard library maintenance and deliverable review task management system

Pie Chart: AZ standards requests



Status

Total Issues: 285

■ Study update approved	149
■ Done	57
■ Rejected	14
■ Library update approved	12
■ More Information Required	13

Activity Stream

Activity Stream

Today



Robert Green changed the status to Under Full Review on AST-314 - Create a new addendum to the UAP

6 hours ago Comment Vote Watch

Robert Green changed the status to Under Full Review on AST-313 - DMP updates

6 hours ago Comment Vote Watch

Yesterday



susan.grootes created AST-314 - Create a new addendum to the UAP

add a new addendum to the UAP indicating the specific permissions in Rave for all roles

Yesterday Comment Vote Watch

susan.grootes created AST-313 - DMP updates

Addition of following text:

'Subject enrolled in error in EDC
The AZ Study Team informs the Covance PDM of a subject enrolled in error in EDC and therefore needs to be deleted from the database. Before the deletion, the following actions must be

Read more » Yesterday Comment Vote Watch

Friday



Robert Green changed the status to Study update approved on AST-312 - addition of LVES and LVED on PSTAT

4 days ago Comment Vote Watch

Robert Green changed the status to Study update approved on AST-311 - collection of start/stop date and time on EG

4 days ago Comment Vote Watch



Pk7719Rr changed the status to Under Full Review on AST-312 - addition of LVES and LVED on PSTAT

4 days ago Comment Vote Watch

Filter Results: Approved library updates

AZ Study ID	T	Summary
Standard		Edit check AZAWSAE_DSALERT_01
D5671C0002 (NASH)		Demographics DOB - allow partial for all countries
D5084C00007 (SAVANNAH)		AECHG - check was incorrectly programmed
Standard		new edit check for ELIG
General Question		AEACNOT's new edit when all 4 AEACNOT's are used
D6401C00004 (MCR)		New edit checks for subject status
D6186C00001 (ORCHARD)		new edits for CM
D6186C00001 (ORCHARD)		new edit check for Serious Adverse Events eCRF
D6186C00001 (ORCHARD)		new edit check for vitals signs eCRF
D5084C00007 (SAVANNAH)		COLMTH - update update 'Broncoscopy' to 'Bronchoscopy'

1-10 of 12

1 2 >



JIRA® – metrics

Issue Type	# Issues	First Response				
		Issues		Time (days)		
		n	(%)	Median	Min	Max
Form Level Update	46	43	93	1	0	3
New Edit Check	27	27	100	1	0	4
New Field on existing form	52	52	100	0.5	0	14
New Form	26	26	100	0.5	0	4
New derivation	3	3	100	1	1	2
Update field on existing form	47	45	96	0	0	3
Update to Codelist	27	25	93	1	0	1
Update to Edit Checks	23	23	100	1	0	5
Update to custom function	3	1	33	0	0	0



Challenges with implementing proposed model

- ▶ Missing TA standards in our library – AZ standards very flexible with many options.
- ▶ Challenging to have a TA standard that study teams could adhere to
- ▶ Mix of experience in the study teams – so staff expectations were different
 - Many voices / opinions to manage
 - Desire to almost ‘over check’ a study
 - Staff turnover influenced delivery expectations
- ▶ Multiple protocol templates – versatile design due to the phase and goal of the study
 - Means discussions and decisions are made at study team meeting (and a tendency to revisit)
 - Managing deviations and decision log is key and challenging
 - Multiple significant protocol amendments to handle
- ▶ Exploratory endpoint data means many external vendors

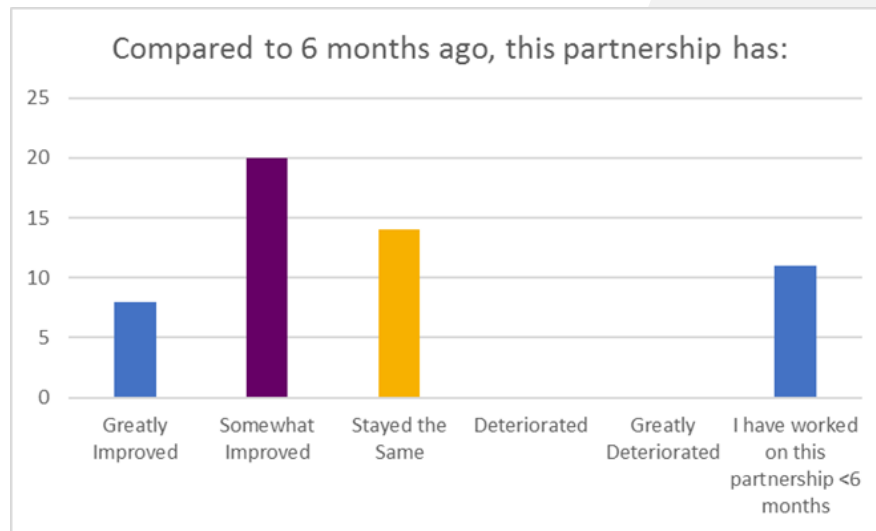
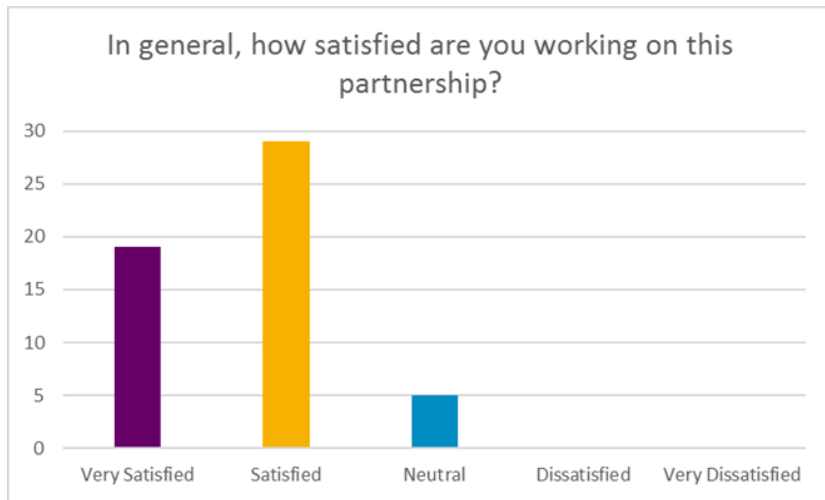


Positive

- ▶ Collaborative partnership - regular meetings at all levels
- ▶ Reward system implemented to recognise key contributions
- ▶ Open communications encouraged
- ▶ lessons learnt activities for all milestones
- ▶ looped back into process improvements and annual objectives
- ▶ Respectful professional relationship
- ▶ escalations handled effectively / objectively
- ▶ Positive experience on both sides
- ▶ Timelines met for study setup – 12 weeks
- ▶ KPIs tracked, reviewed quarterly
- ▶ Audit feedback has been good so far
- ▶ Survey data collected across the partnership

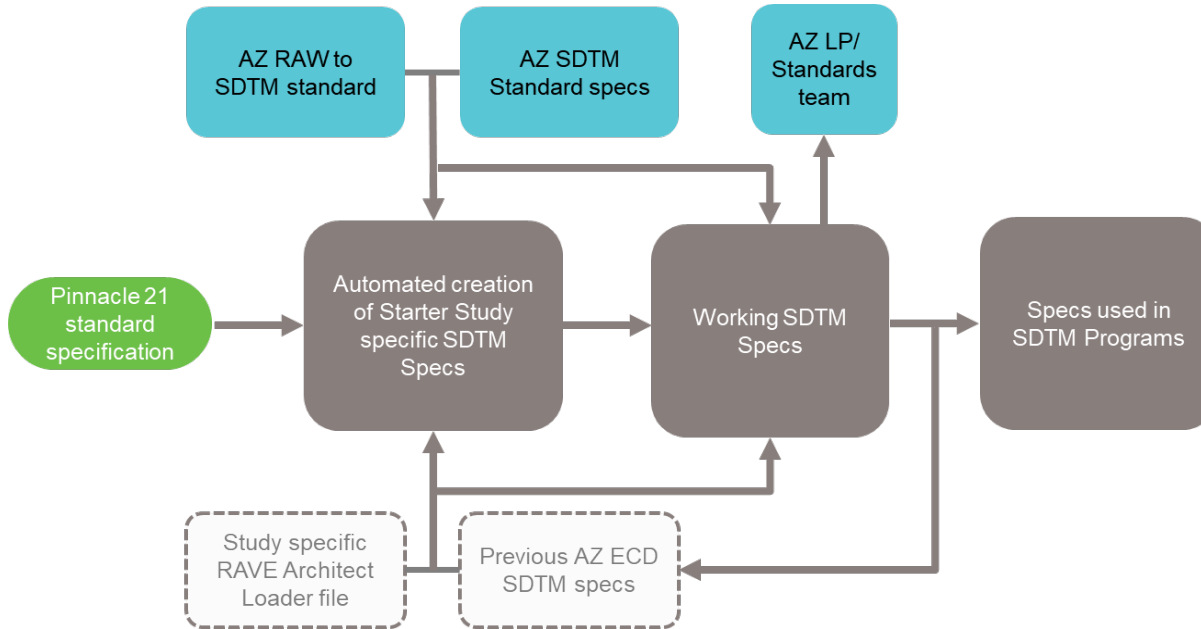


2019 Key Survey Results



Updated SDTM mapping plan

AZ Raw Data Standards and Mapping



Automated Mapping to SDTM

- ▶ The creation of working SDTM specifications is done programmatically, by a program that uses information from earlier studies.
- ▶ Programmers only interact with the system via the SDTM specifications
- ▶ Every handled study adds to the knowledgebase used by this program. Continuously increasing the variation in RAVE databases that it can cover.



Challenges Faced

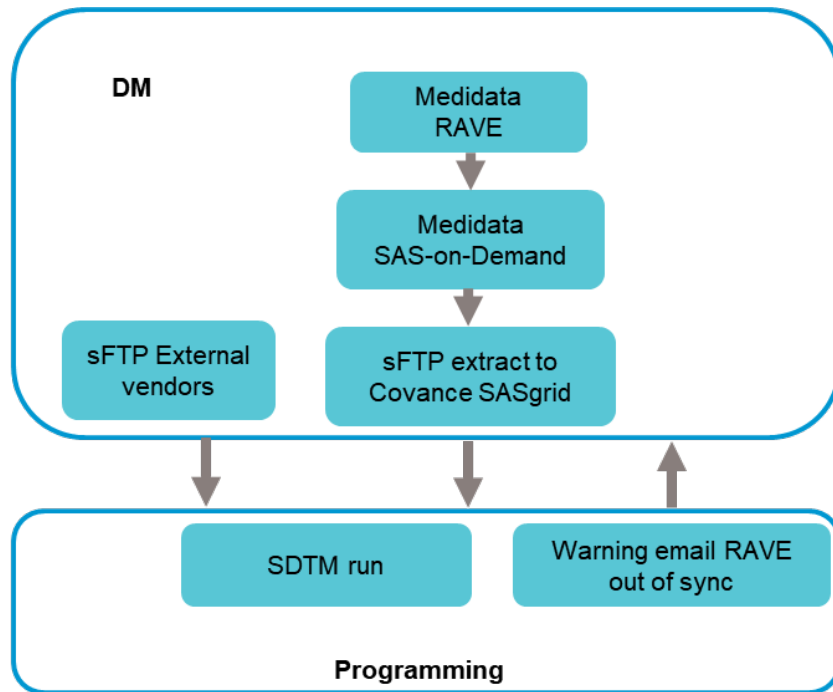
Data flow into SDTM

- ▶ One of the goals in this partnerships was enabling daily SDTM transfers
- ▶ Reduce time of data entry and availability of that data on AZ systems via SDTM.
- ▶ As it's daily, it needs to be fully automated
- ▶ several systems that must be in sync with each other to minimize data lag.
- ▶ Initially, there was a lack of insight on RAVE data status.



Challenges Faced

Data flow into to SDTM



Challenges Faced

Data flow into to SDTM

ZIP is one day older than transfer from RAVE sFTP, zip= 2019-10-16 sFTP= 2019-10-17

ZIP is one day old: 2019-10-16

Multiple zip files (2) in one day, unclear what was unzipped

ZIP is one day old: 2019-10-01



Challenges Faced

Daily SDTM runs and ongoing data

- ▶ Ongoing data can have its imperfections.
- ▶ This can lead to issues in SDTM creation
- ▶ If left unsolved, it could even stop the daily SDTM transfers

- ▶ Needed a solution that streamlines communication between DM and programming



Challenges Faced

DAILY SDTM runs and ongoing data

```
%export_finding_report( inds      =lab_rave_ext_mismatch  
                        ,finding_spec=External Lab data but no sample in RAVE  
                        ,finding_type=MAJOR  
                        ,source_type =EXTERNAL  
                        ,source_spec =LAB  
                        ,keep_var   =subject foldername);
```

A	B	C	D	E	F
FINDING_SPEC	FINDING_TYPE	SOURCE_TYPE	SOURCE_SPEC	SUBJECT	FOLDERNAME
ExternalLAB data but no sample in RAVE	MAJOR	EXTERNAL	LAB	xxxxx	Visit 2



Medidata Rave® Lab Module

Lab Administration

- Analytes
- Central Labs
- Clinical Significance Codes
- Global Data Dictionaries
- Global Labs
- Global Unit Dictionaries
- Global Variables
- Lab Units
- Lab Unit Dictionaries
- Range Types
- Standard Groups
- Unit Conversions

Analyte dictionary

Unit dictionary

Unit conversion dictionary

Lab analyte unit look up dictionary

Normal Range entered for each site, selecting the correct analyte unit combination

Sites select the correct normal range

Subject: RFS654
Page: Hematology 15 Jan 2008 - Labs (1)

Lab: Analysis, Inc. Lab Edit Ranges

Analysis Date: 15 JAN 2008

	Data	Range Status	Unit	Range	
WBC	4.9		*10E3/uL	3.5 - 12.5	
RBC	3.4		*10E6/uL	3.5 - 12.5	

Clinical Significance: ...

Rave applies the range to the entered data, displays the status and requests the sites enter clinical significance



Challenges Faced

Rave Lab Module

- ▶ RAVE LAB module removes a lot of local lab issues by providing a clear framework and metadata driven data-entry.
- ▶ Issues in the metadata, or data-entry can still occur, and we created a SAS process to guide reviewers:
 - 1) Check whether the site have specified their lab name
 - 2) Per site, check how many results were entered without raw units
 - 3) Per site/analyte, check how many results with raw units lack standard units
 - 4) Per analyte, check all standardized normal ranges against each other.
 - 5) Per analyte, check the Coefficient of Variation of the raw unit summaries versus the Coefficient of variation of the standardized value
 - 6) Per analyte, an outlier analysis / top / bottom 5 for the more generic data checks



Challenges faced RAVE LAB MODULE

PER ANALYTE, CHECK ALL STANDARDIZED NORMAL RANGES AGAINST EACH OTHER.

Parameter (SI unit)	Limit of normal			Mag. Diff
	Lower	Upper	Midpoint	
X (pmol/L)	0.9009	1.9305	1.4157	
X (pmol/L)	10	20	15	1
X (pmol/L)	70785	141570	106177.5	5



Challenges faced RAVE LAB MODULE

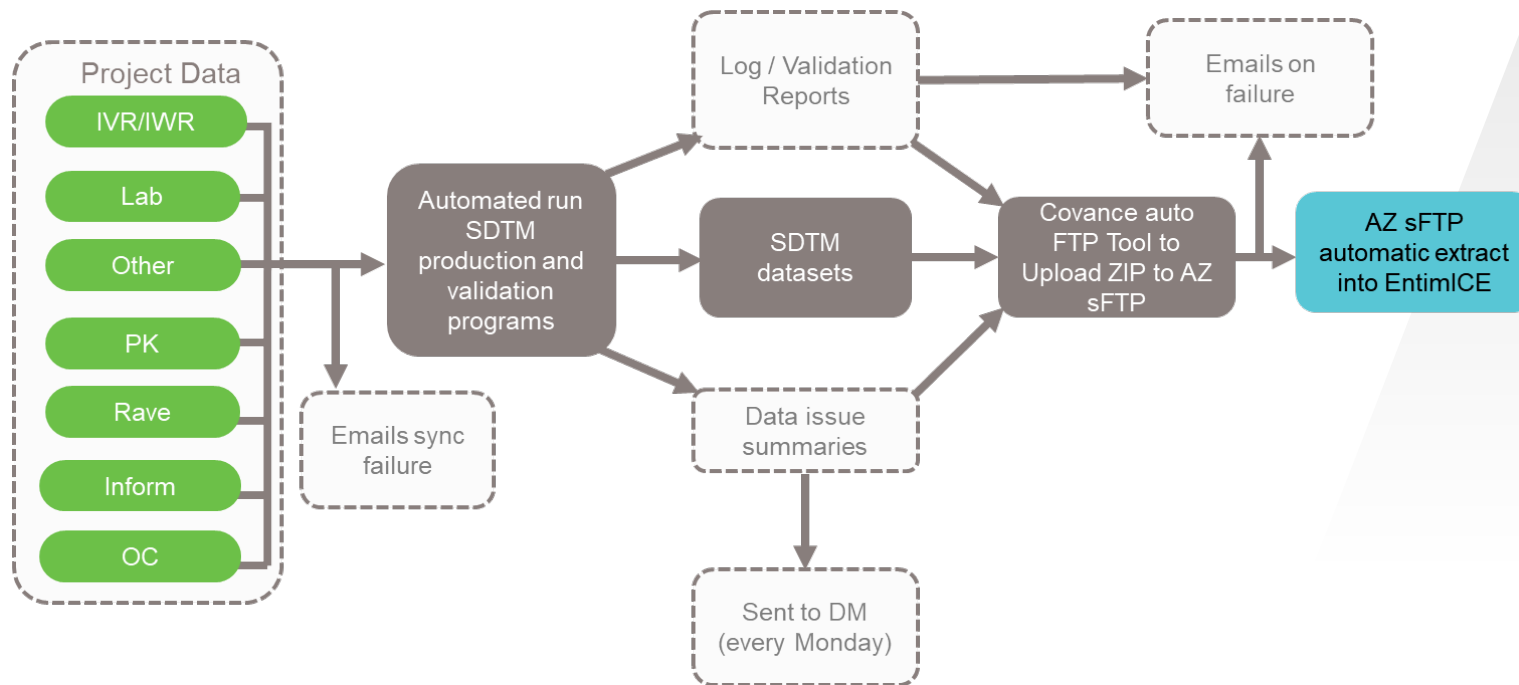
THE COEFFICIENT OF VARIATION INCREASES

Unit_type	Unit	CV
raw	INR	33.6718
raw	[ratio]	20.6619
std	[ratio]	430.9422



Challenges Faced

DELIVERY OF DAILY SDTM



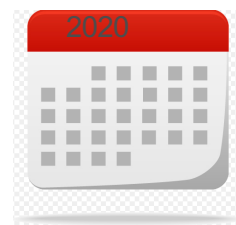
What the Future Looks Like?



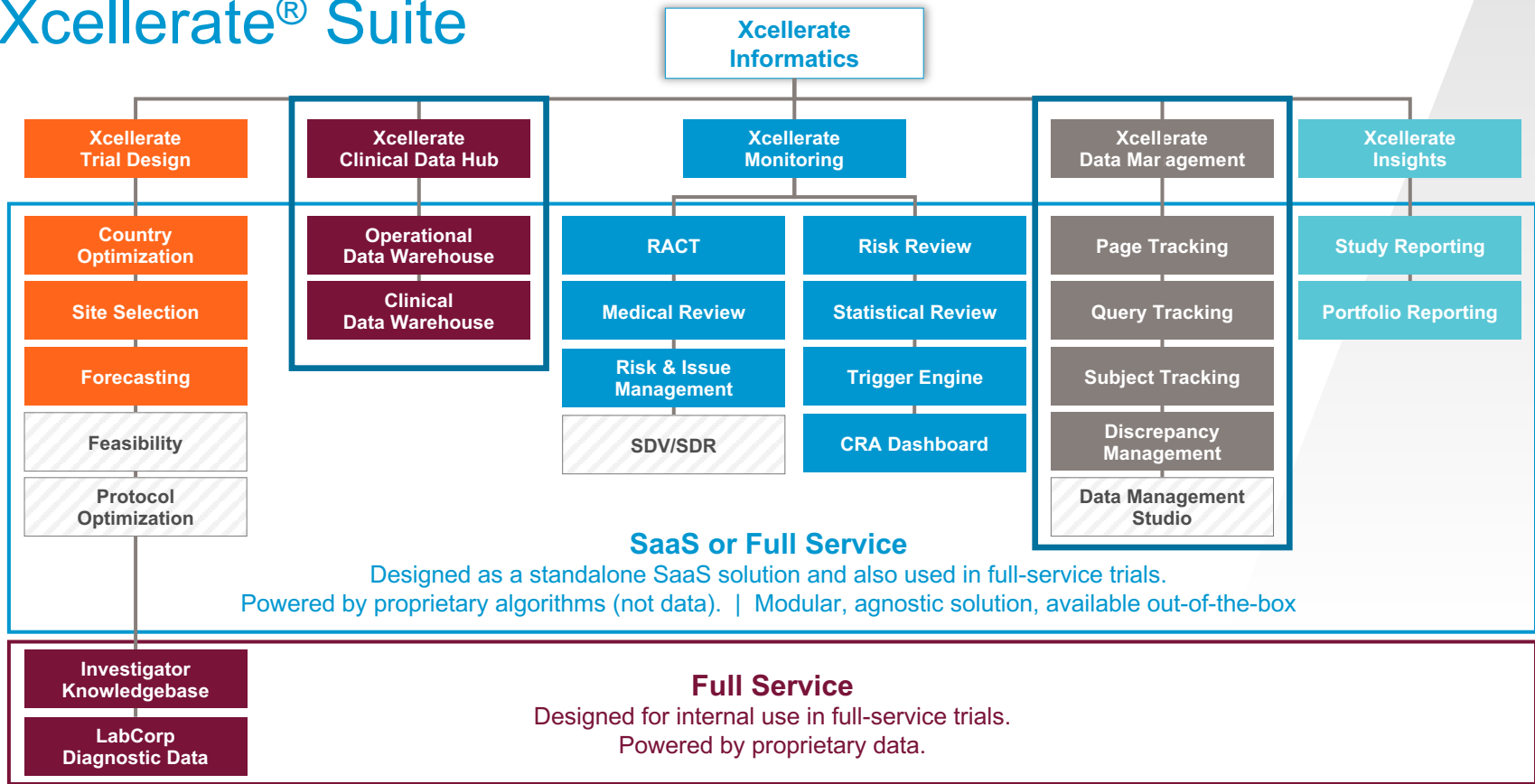
The near future

Our Areas of Focus include

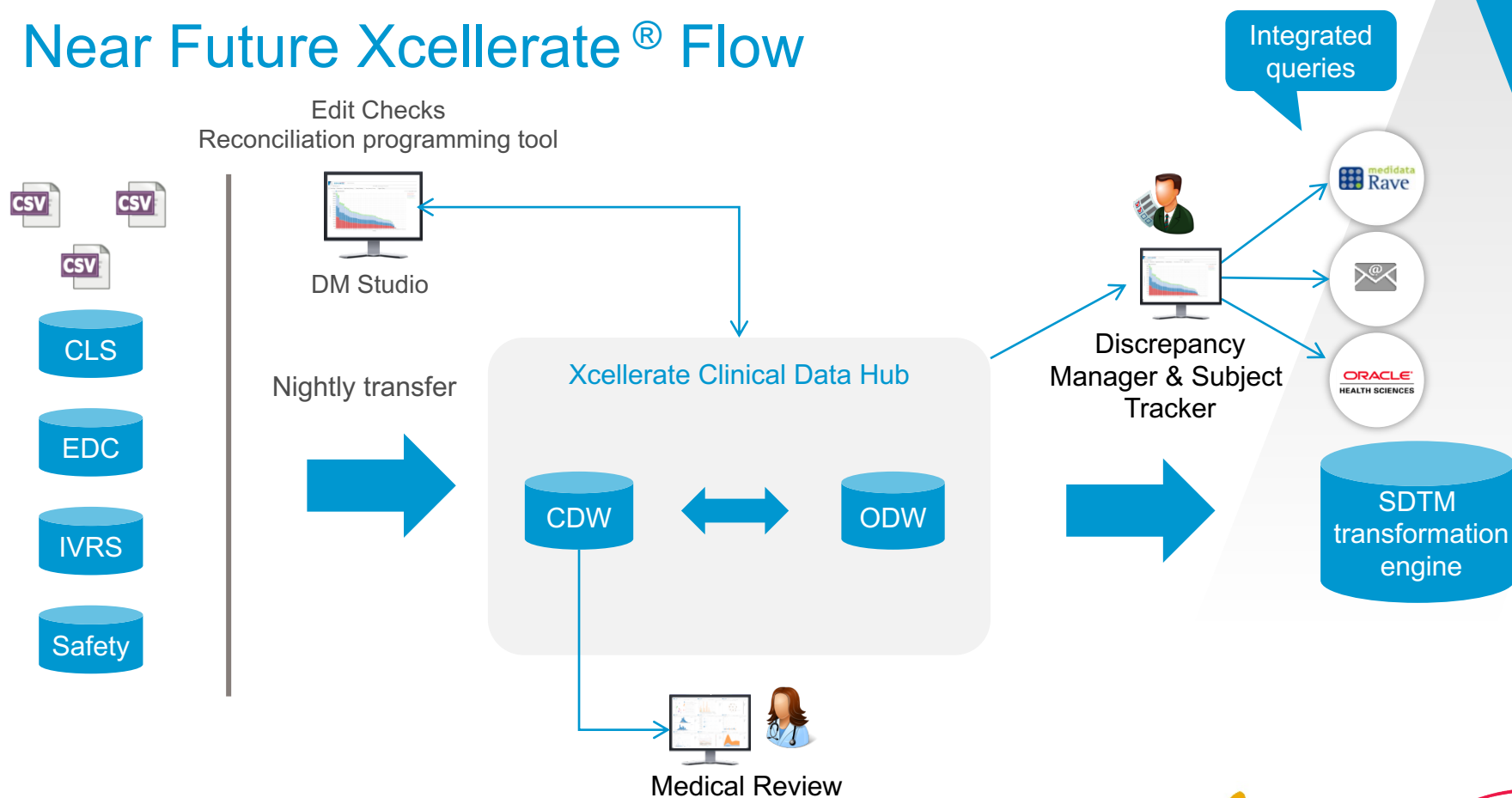
- ▶ External Data – goal to handle in a similar timeframe to EDC collected data
- ▶ Nightly transfers of laboratory data
- ▶ Implement a data warehouse to house all data
- ▶ Automate the load and review of external data
- ▶ Reconciliation programming to be moved to our data warehouse
- ▶ Automate the handling of SDTM generated data issues



Xcellerate® Suite



Near Future Xcellerate® Flow



Conclusion

Delivered on our original Goal 'Get Closer to the Data'
Positive experience from both organisations
Recent audit feedback supports this success

Highlighted areas where we can enhance our knowledge
Building on our initial plan for a standards led approach.
Look towards future innovations



Thank You!!!

Contact



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