
Rare diseases - The challenges of programming novel Clinical Outcome Assessment (COA) endpoints

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Agenda

- Introduction
- Background of example studies & experience
- Challenges & resolutions of programming:
 - New disease areas
 - Novel endpoints
 - Clinical Outcome assessments(COA)
- Extra challenges of electronic Clinical Outcome Assessments (eCOA)
- Conclusion - How it all interlinked and outcome

Disclaimer

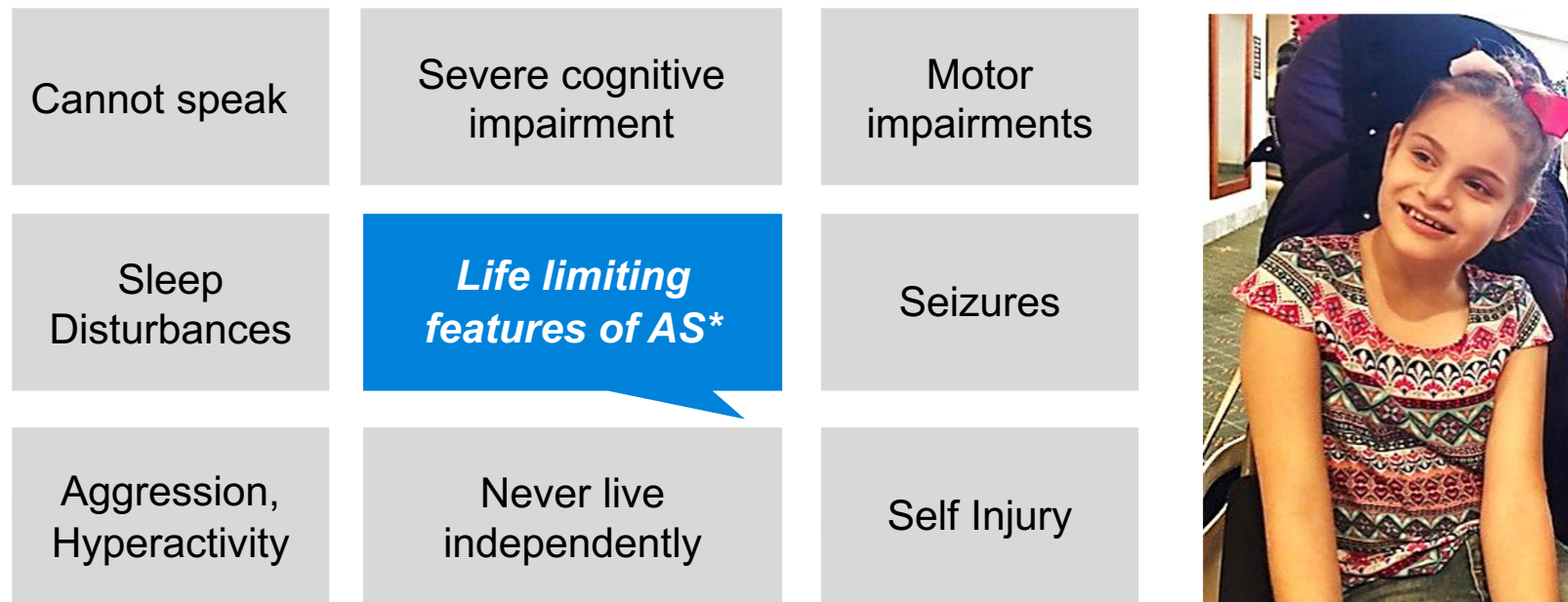
- This is all based on my experience and not reflective of Roche or Pharma as a whole.
- This presentation is aimed to show the challenges that one can face when programming SDTMv, ADaM and/or outputs, with regards to novel disease areas, endpoints or scales & eCOA. Based on one experience
- As this scope is quite large, we will only be touching the surface and hopefully can entice some discussion

Background – Two Angelman Syndrome (AS) studies

FREESIAS (BP40654)	TANGELO (BP41674)
Phase 1	Phase 1
Observational study	Study drug (Dose escalation)
Typical development vs UBE3A deletion present vs UBE3A deletion not present	AS population
Grouped by age groups	Grouped by age groups (all paediatric)
Questionnaires include: Vineland-III, Bayley-III, HOST, SNAKE, Seizure diary, Sleep diary, CGI-S, ABC, Communication matrix, PEDSQL, etc.	
Questionnaires collected on eCRF	Questionnaires collected in eCOA device

Rare diseases - What is Angelman Syndrome?

- A severely debilitating neurodevelopmental disorder with high unmet need
- Incidence **~1:12-20,000 births***
- Severe disease with no approved therapy available: **24 hour care required throughout life**



Clinician and caregiver input reported in a Roche sponsored study conducted in the US and NL

*Mertz *et al.*, 2013 and Petersen *et al.*, 1995

Rare diseases - Difficulties and challenges with new (rare) disease areas

Scientific and statistical knowledge:

- Unknown endpoint, so multiple duplicate scales used, e.g Communication Matrix and Bayley's
- Limited experience in understanding of scales (not much crossover of scales)
 - ADaM and TLGs require knowledge. SDTM require controlled terminology
- Study challenges
 - Challenges of recruitment,
 - Patient population
 - COVID-19 impact – Lumbar puncture, Hospital visits, PPE
- Difficult patient population means different Schedule of Assessments – e.g. less assessments
 - Crossover of patients between studies, crossover of visits to avoid duplication.

Rare diseases - How were these challenges resolved

- Closer collaboration with other groups within organisation
 - Operational (timelines),
 - Science (understanding of disease background and scales),
 - Data Standards (new codelists),
 - Data Management (collection of data)
 - Biostatistics (analysis required)
 - Patient Centered Outcomes Research (PCOR) (COA experts)
- Reading papers
- Search engines

COA – What is it?

**Patient reported
outcome (PRO)**



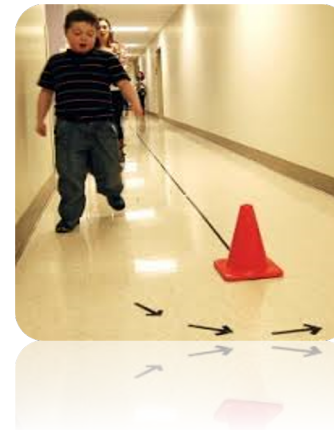
**Observer reported
outcome (ObsRO)**



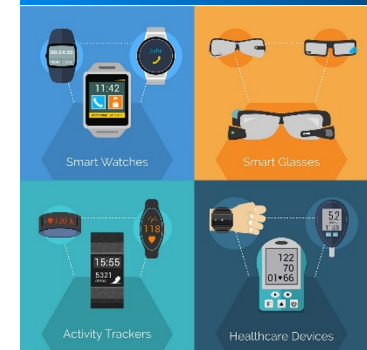
**Clinician reported
outcome (ClinRO)**



**Performance
outcome (PerfO)**



**Digital
monitoring
COAs**



COA – Bayley-III & Vineland-III



- Assesses child development on 5 scales:
 - Language
 - Adaptive
 - Social-emotional
 - Motor skills
 - Cognitive



- Individual assessment of adaptive behaviour on 4 domains:
 - Communication
 - Daily Living Skills
 - Socialisation
 - Motor skills

COA -Difficulties of Programming Bayleys and Vineland

Decision to do Bayleys and Vineland summary scores programming in-house. Difficulty programming:

- Raw scores
- Age comparisons
- Compliance calculations

COA – ADaM ADQS Subdomain Raw scores

Raw Scores

- Raw scores most difficult, as many imputation rules.
- Each subdomain begins at investigator discretion.
- There are many rules, the Biggest being assigning basal and ceiling (beginning and end) Vineland assumption (e.g. last four 2's, first four 0's) 2 before, 0 after . Many considerations
- Challenges with programming:
 - Different basals & ceilings (not flagged)
 - Different start and end points
 - Inputting data outside of window
 - When data is missing?

COA – ADaM ADQS Subdomain Raw scores

- Resolution:
 - Combine with all expected questions to get order and any missing or non-answered Q's
 - Set basal and Set 2's prior
 - Set ceiling flag and 0's following
 - Sum total scores
- How to deal with all scenarios
 - Ceiling prior to basal
 - No basal/ceiling
 - Handling of missing data between
- Recommendations
 - Use good programming practices - proactive programming(warnings), useful comments
 - Google! (or your preferred search engine)
 - Use CDISC ADQS guidance - mainly flags

COA – ADaM ADQS other complexities

Age standardised scores.

- Comparison of standard scores with age comparison
- 525 page PDF document to XML – R macro (work-in-progress)
- Programming comparable values – macro to fill in ranges
- Per age group (some 30 day intervals)
- AS patient comparison unknown

Table B.1 v-Scale Score Norms for Subdomains: Comprehensive Interview Form, Ages 0:8:0–0:8:30

v-Scale score	Communication			Daily Living Skills			Socialization			Motor Skills		v-Scale score
	rec	exp	wrn	per	dom	cmm	lpr	pla	cop	gmo	fmo	
1	—	0–1		—			0–1	—		—	—	1
2	—	2		—			2	—		—	0	2
3	0	—		—			3	—		0	1	3
4	1	3		—			4	—		—	2	4
5	—	4		—			5	0		1	3	5
6	2	—		0			6	—		2	—	6
7	3	5		—			7	1		3	4	7
8	4–5	—		1			8–9	2		4	5	8
9	6	6		2			10–11	3		5	6	9
10	7	7		3			12–13	4		6	7	10
11	8	8		—			14–15	5		7	8	11
12	—	9		4			16–17	—		8	9	12
13	9	10		5			18–19	6		9	10	13
14	10	11		6			20	7		10–11	11	14
15	11–12	12–13		7–8			21–22	8		12–13	12	15
16	13	14		9			23–24	9–10		14–15	13–14	16
17	14–15	15		10			25–26	11		16–17	15	17
18	16–18	16–17		11–12			27–29	12–13		18–20	16–17	18
19	19–21	18–19		13–14			30–32	14–16		21–23	18	19
20	22–25	20–22		15–17			33–36	17–19		24–26	19–20	20
21	26–29	23–25		18–20			37–40	20–22		27–29	21–22	21
22	30–33	26–29		21–24			41–44	23–25		30–33	23–24	22
23	34–37	30–32		25–28			45–48	26–28		34–37	25–26	23
24	38–78	33–98		29–110			49–86	29–72		38–86	27–68	24

COA – ADaM ADQS other complexities

Compliance questions

- Adding compliance parameters
- Ceiling present,
- Basal present
- Etc.

PARAM	PARAMCD	PARCAT1	PARCAT2	PARCAT3	AVAL	AVALC
Cognitive, must have only 1 result per question	COCOGEN0	BAYLEY SCALE...	COMPLIANCE		1	CRITERION MET
Cognitive, must have no results after a sequence of 5 consecutive values of 0	COCOGEN1	BAYLEY SCALE...	COMPLIANCE		1	CRITERION MET
Cognitive, must have no positive results after a sequence of 5 consecutive values of 0	COCOGEN5	BAYLEY SCALE...	COMPLIANCE		1	CRITERION MET
Cognitive, must end with 5 consecutive values of 0	COCOGMIS	BAYLEY SCALE...	COMPLIANCE		1	CRITERION MET
Cognitive, must not miss questions in the middle of assessment range	COCOGST3	BAYLEY SCALE...	COMPLIANCE		1	CRITERION MET
Fine Motor, must have only 1 result per question	COFMOEN0	BAYLEY SCALE...	COMPLIANCE		1	CRITERION MET
Fine Motor, must have no results after a sequence of 5 consecutive values of 0						

Novel endpoints -Difficulties of programming novel endpoints

- Having new scales means more novel endpoints. For Tangelo, the efficacy endpoints were broad, (e.g. “To characterize changes in...”).
- More exploratory work needed to determine how this data should be visualised. These issues included:
 - Challenging, unique graphs
 - More outputs, to determine which would be most useful.

Novel endpoints –Tips and resolutions of issues.

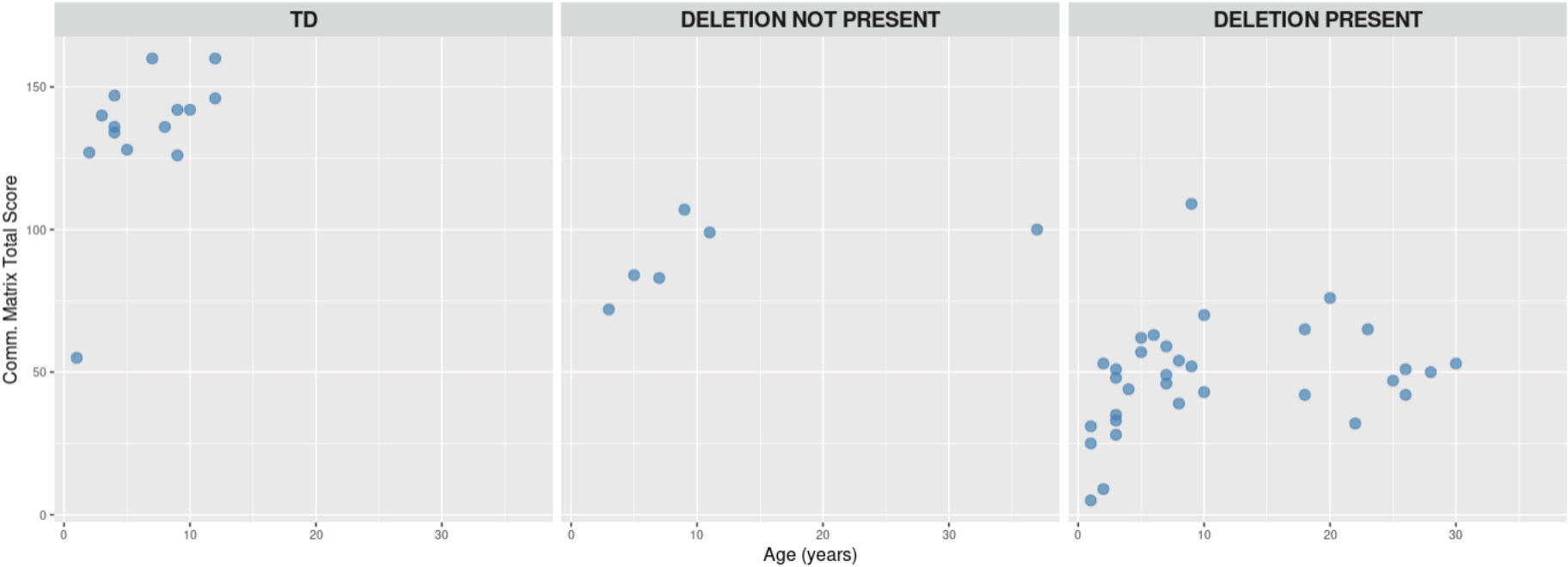


To adapt to the exploratory nature of the outputs, we created a R shiny app, with multiple graphs and visualisations on the same data, to try understand and specify which would be the most useful.

UBE3A FREESIAS – Exploratory Data Analysis



Total raw score by GENTYP and Age



UBE3A FREESIAS – Exploratory Data Analysis



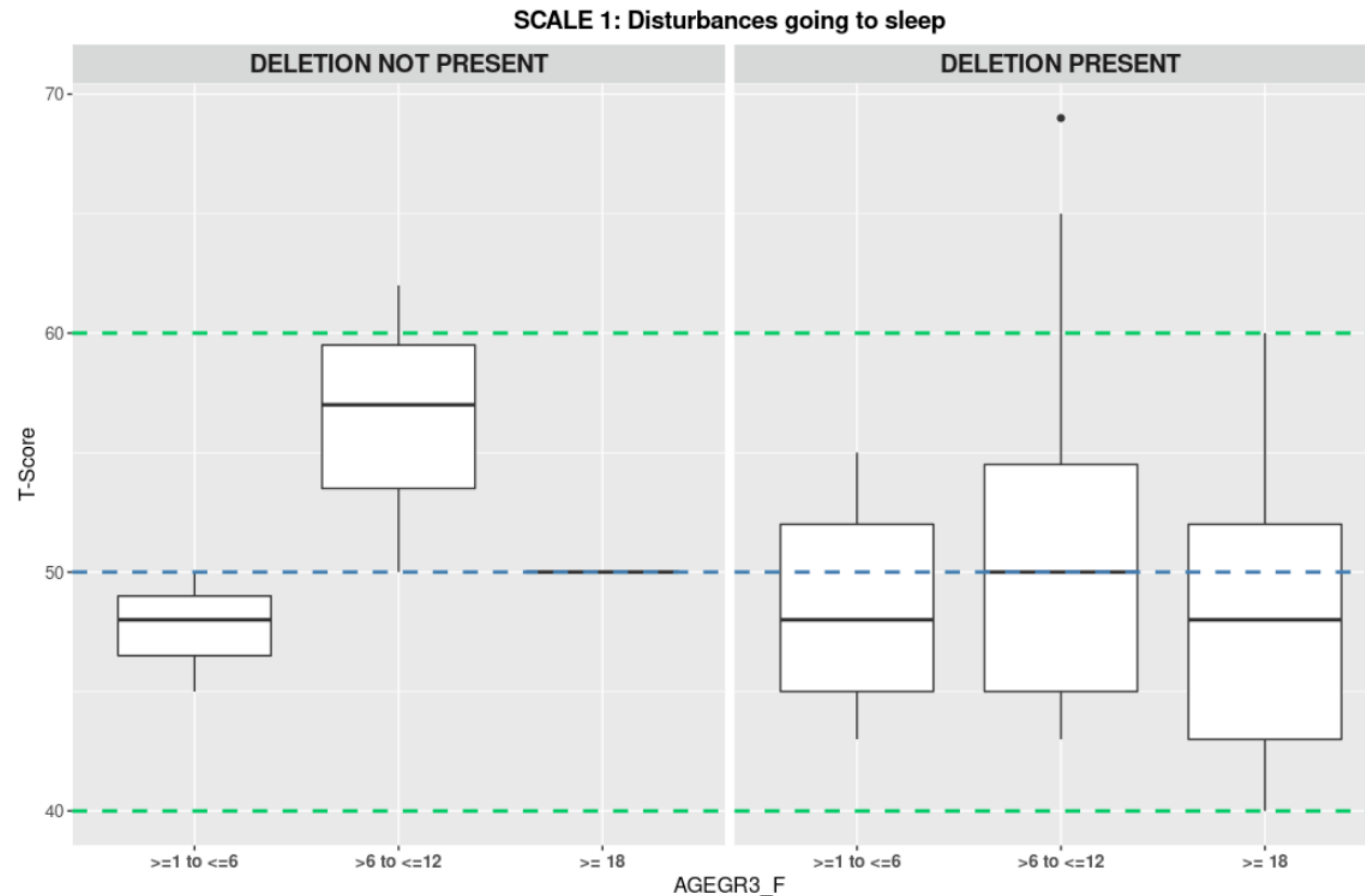
Subscale 1 Irritability – Distribution of Scores for each question by GENTYP



UBE3A FREESIAS – Exploratory Data Analysis

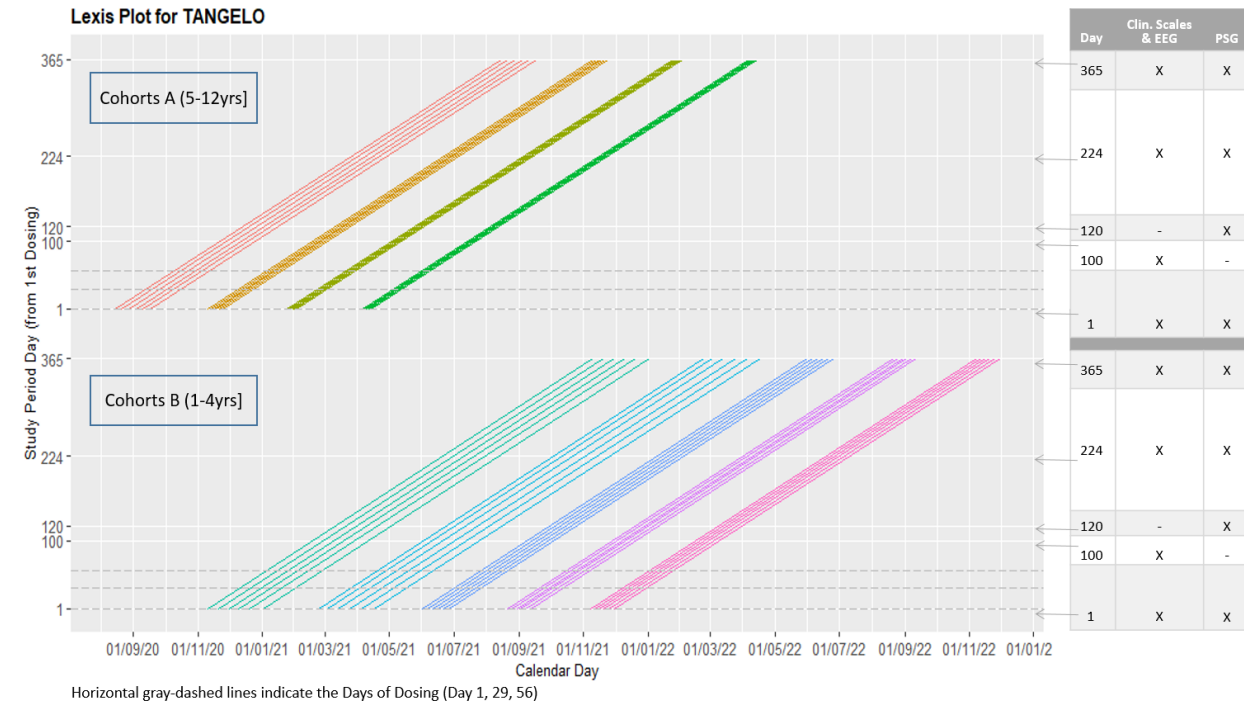
Component VI – Symptoms and consequences of sleep disorders

Scale 1 – Disturbances going to sleep – T-scores – by AGE group and GENTYP



Novel endpoints - Exploratory Data Analysis

- Genotype, Age, Subject
- Patient reports
- Standardised scores, raw scores
- Questionnaires, Domains, Subdomains, item level
- Study information
 - Number of missing items
 - Lexis plots, patient information
- We reused much of the code in a validated R system to create final static outputs.
 - SDTM, ADaM ,Tables and listings in SAS.
 - 270 Graphs in R

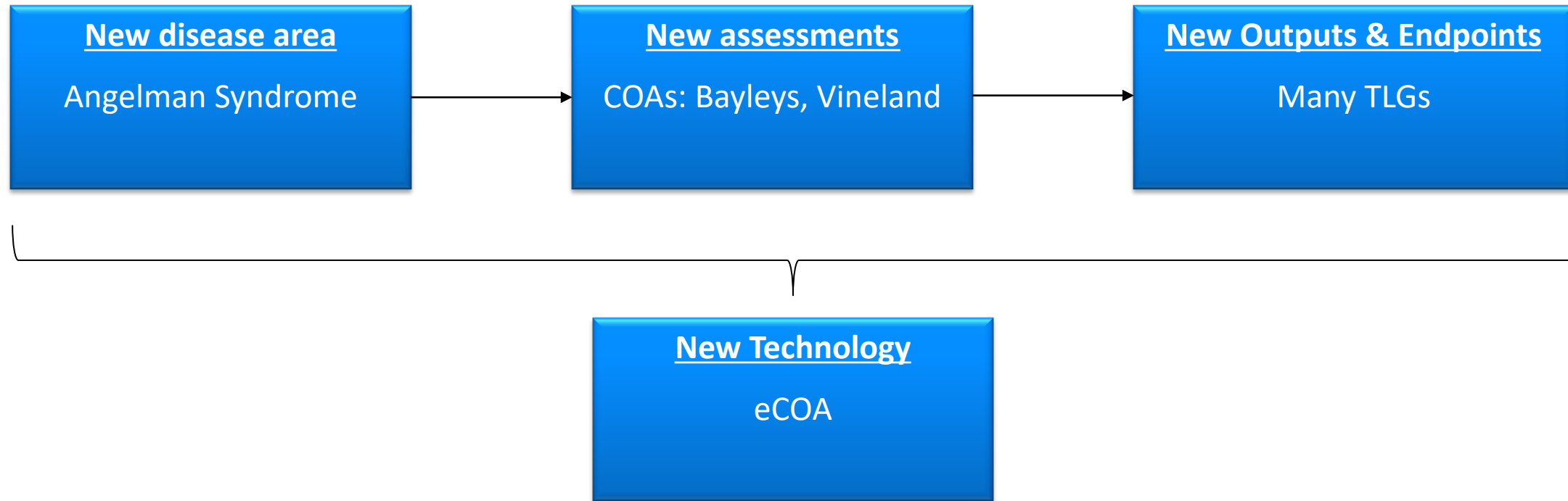


eCOA - What challenges did it present?

eCOA was used on Tangelo to collect questionnaires, scales & diaries. Presented it's own challenges:

- Dates and times for non-completed records
- Missing questions
- Added layer of complexity of changing collection
- More data than sometimes required.
- Difficult imputation rules (e.g. what was mentioned before)
- SDTM considerations – Pooling of data (consistency),

Overall picture



- Novelty breeds exploration, innovation and experimentation
- Resolve challenges with explore new ways of working: IDD, Scientific and statistical research, complex code, reuse of code, different languages

Acknowledgements

- Roche - Angelman Syndrome Study Management Teams
- Intego Group- SPA business partners
- Cogstate - eCOA vendor

***Doing now what patients need
next***