Standards and Open-Source Hand-in-Hand: Leveraging Automation to Expedite Drug Market Request Review Process

Angelo Tinazzi, Cytel Inc.

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Angelo Tinazzi is Senior Director, Statistical Programming, responsible for Clinical Data Standards and Data Submission at Cytel.

He is a well-published and recognized expert in statistical programming and data standards with over 25 years' experience working with different organizations in Italy, UK, and Switzerland.

Angelo is an authorized CDISC ADaM instructor, stream chair for PHUSE-EU, committee member of the CDISC European Committee, where he also manages the Italian-speaking CDISC User Network.

Since 2018 he maintains a Cytel blog “The Good Data Submission Doctor” https://www.cytel.com/blog/author/angelo-tinazzi

My journey so far

Born in Milan (Italy) sometimes in ’70….

Football

Fashion

History

My journey so far

Born in Milan (Italy) sometimes in ’70…. In what is considered today the Milan Chinatown

It is the oldest and largest Chinese community in Italy, with about 21,000 people in 2011

Originally established in via Canonica in the 1920s, used to operate small textile and leather workshops

Today the district is filled with hairdressing salons, fashion boutiques, silk and leather stores, libraries, traveling agencies, medicine centres and massage parlours

My journey so far

Grew-up and studied in Milan (Statistics)

Professionally grew-up at Mario Negri Pharmacological Institute in the nineties
- Discovered Clinical Trials
- Discovered the beauty of Clinical Data and SAS

Fine-tuned **Computer science applied to Stats in Cambridge, UK, late ’90**

Joined Pharma Industry in 2000 (Pharmacia & Upjohn)

Discovered CDISC in 2003

Emigrated in Switzerland, Geneva in 2008, Working for Merck Serono
- Failed some submissions

Joined Cytel in 2012
- Successfully submitted first time in 2013
- Lost the count of how many submissions, mostly successful

Live in France (Ferney Voltaire) **since 2010**
- Crossing the border to go to work in Geneva everyday

Meanwhile **one wife and three kids** (21, 12, 10)

Agenda

- 01 **Preview of Data Submission in 2041**
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- 02 **2023 targeting 2041**
- 03 **Standards and Open-Source Initiatives**
- 04 **Final Remarks**

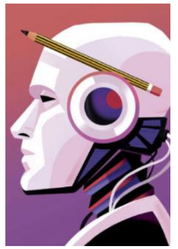
Cytel

Imagine Data Submission in 2041, what do you see?

From: **AI 2041**, Kai-Fu Lee – Chen Qiufan

Summary of stories discussed, technologies hypothesis

Imagine Data Submission in 2041, what do you see?



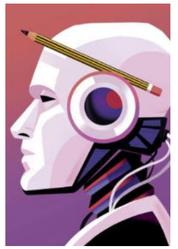
A Reviewer stepping into your lab through a visor checking your data and results?

An IA doing the submission for you and discussing with the reviewer?

An IA reviewer?

An xD / Multidimensional Database? Well, that’s already possible

Let’s go back to 2023
What are we doing today to target 2041 vision?



NEW DATA STANDARDS

OPEN SOURCES INITIATIVES

NEW TECHNOLOGIES

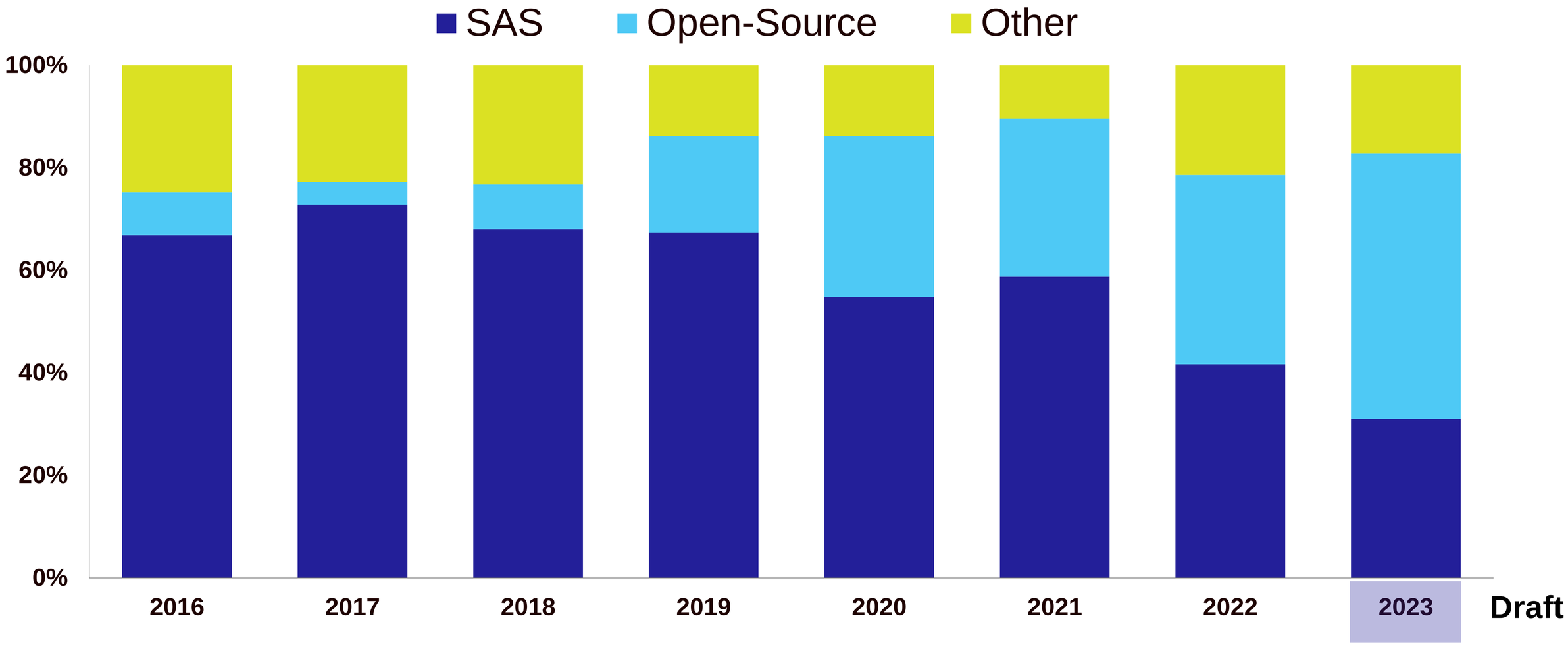
Let’s go back to 2023 Some attempts
What are we doing today to target 2041 vision?

Let’s go back to 2023
Open-Source Initiatives – FDA Statement

Statistical Software Clarifying Statement

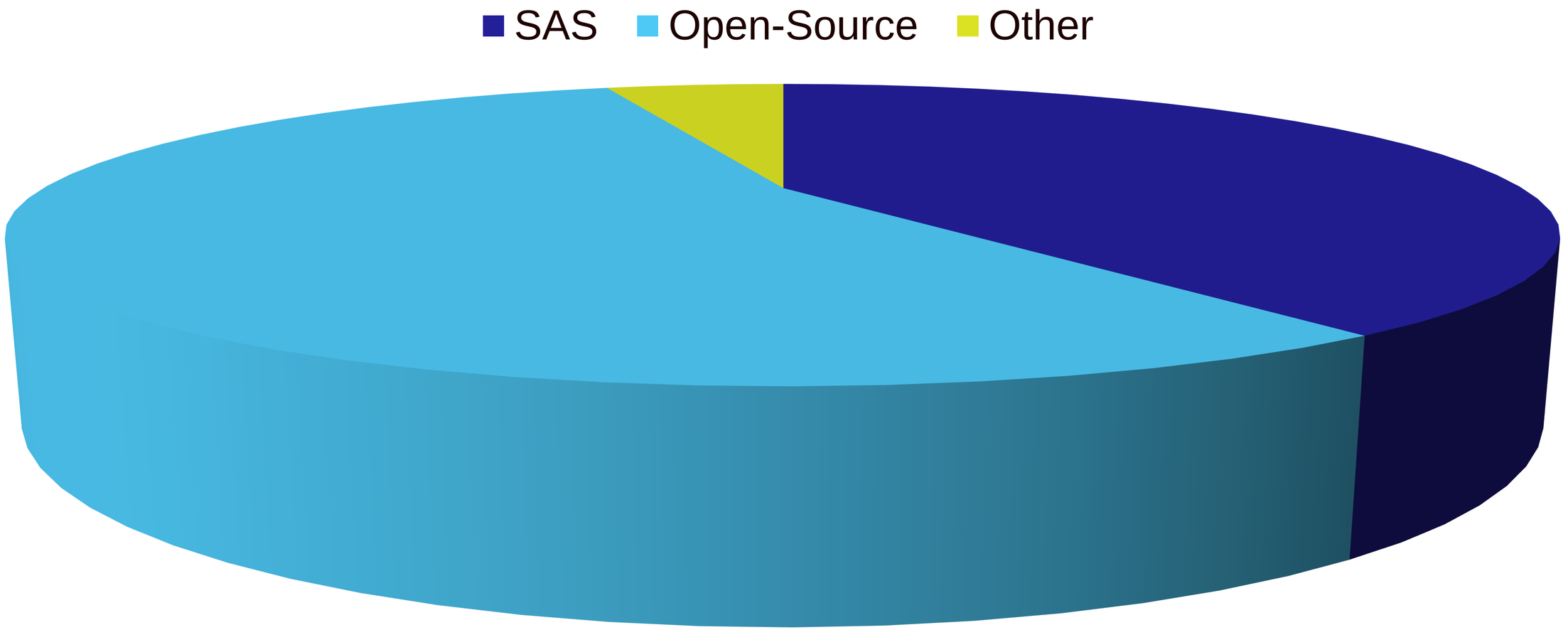
FDA does not require use of any specific software for statistical analyses, and statistical software is not explicitly discussed in Title 21 of the Code of Federal Regulations [e.g., in 21CFR part 11]. However, the software package(s) used for statistical analyses should be fully documented in the submission, including version and build identification.

Let’s go back to 2023
Open-Source Initiatives – A change already occurred



PHUSE EU 2016-2023 Presentations showing or discussing SAS, Open-Source or other tools

Let’s go back to 2023
Open-Source Initiatives – A change already occurred



PHARMASUG – CHINA 2023 ….. THIS CONFERENCE

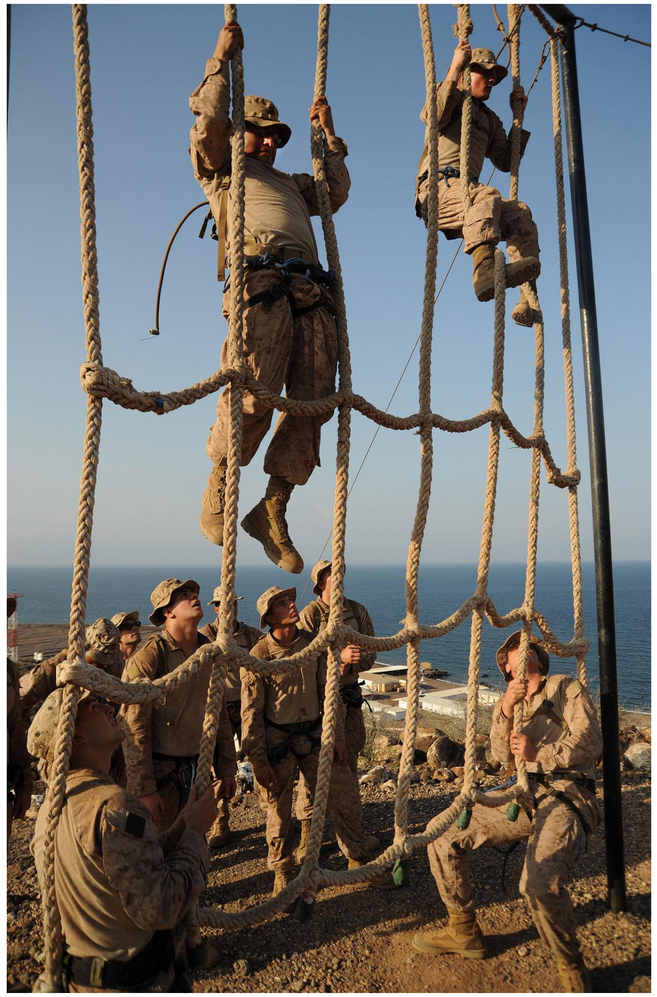
2023 → 2041 Collaboration
A Paradigm Change – What is our Product?

Sponsor aim to get market approval for their products

- A new Device
- A new Drug

A software, a SAS macro, an R library is not what a sponsor wants to make money from

2023 → 2041 Obstacles



- ✓ Collaboration
- × Data Format
- → still submitting 
- × “Dynamic/Interactive” submission

2041? Or may be earlier “Dynamic/Interactive”

A good example “The R Pilot Submission Experience”

Pilot 1

Demonstrate data packages can be created using other software e.g., R

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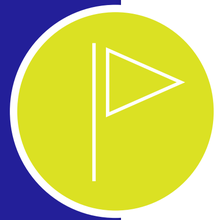
- Ut vulputate lorem in est euismod egestas.
- Pellentesque ultrices velit eu lorem porta ultricies.

Pilot 2

Sharing R Packages

- Include data visualization
- Provide tool the HA can re-use work with it
- Installing and using Sponsor R packages

Outcome



Sed id mauris ac ex gravida porttitor

- Sed vitae nulla varius, mattis massa id, gravida quam.
- Donec nec enim quis ex venenatis scelerisque.
- Phasellus eu ipsum convallis leo imperdiet faucibus ut ac ante.

2041? Or may be earlier “Dynamic/Interactive”
A good example “The R Pilot Submission Experience”

https://github.com/RConsortium/submissions-pilot1-to-fda

FDA can receive submission with R code/packages

R Consortium R Submission Pilot 1

- Objective: to test the concept that an R-language-based submission package can meet the needs and the expectations of the FDA reviewers, including assessing code review and analyses reproducibility.
- Evaluating FDA’s acceptance of system/software validation evidence is not in the scope of this pilot.
- All submission materials and communications from this pilot are publicly available. (Link)

Install Sponsor Packages and reproduced

R Consortium R Submission Pilot 1

- Receive electronic submission package in eCTD approved formats.
- Reconstruct and load the submitted sponsor-developed R package.
- Install and load open-source packages used in this submission.
- Reproduce the analysis results.
- Share potential improvements for submission deliverables and processes via written communications.

Submitted Material

R Consortium R Submission Pilot 1

- What R consortium submitted:
  - ADaM datasets (.xpt files)
  - A pdf report with 4 analysis outputs
  - Analysis Data Reviewer’s Guide (ADRG)
  - Analysis output programs (.r files)
  - Sponsor developed R package (.txt file)

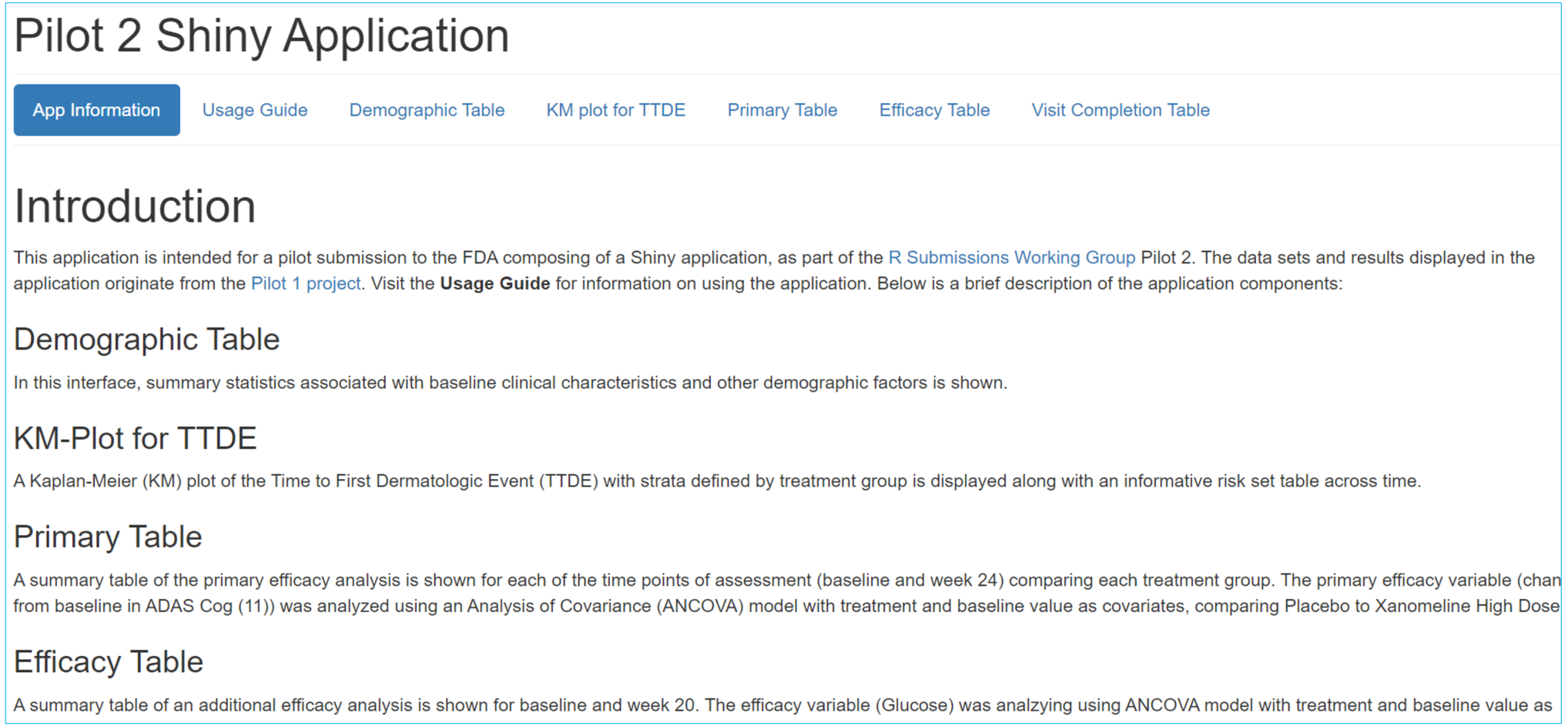
FDA Feedback

R Consortium R Submission Pilot 1

- Using R version 4.1.1, FDA was able to run the submitted code and confirm the submitted tables and figures.
- Using FDA developed code, FDA was able to independently generate tables and figures using the submitted data.
- There were minor issues.
  - Rounding issue
  - Important information was not given in the table

2041? Or may be earlier “Dynamic/Interactive”
A good example “The R Pilot Submission Experience”

https://rconsortium.shinyapps.io/submissions-pilot2/



2041? Or may be earlier “Dynamic/Interactive”
A good example “The R Pilot Submission Experience”

https://rconsortium.shinyapps.io/submissions-pilot2/

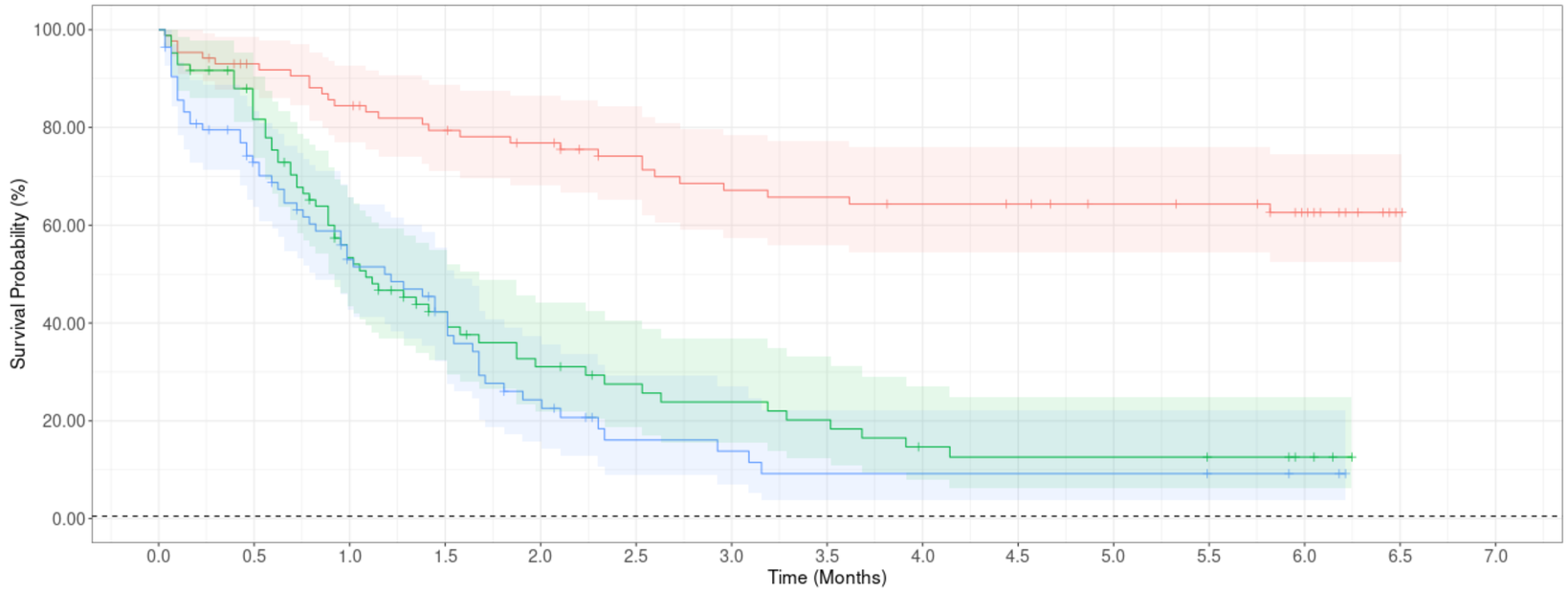
Pilot 2 Shiny Application

App Information | Usage Guide | Demographic Table | **KM plot for TTDE** | Primary Table | Efficacy Table | Visit Completion Table

Important Information:
The analyses performed when utilizing subgroups or other subsets of the source data sets are considered **exploratory.**

- Treatment information variables from the **ADTTE** data set are excluded from the variable list. Use the treatment variables present in the **ADSL** set to perform treatment-related filters.
- In rare situations, applying filters with variables from both **ADSL** and **ADTTE** that overlap in content could result in an invalid data subset. When possible, select variables with distinct content.

KM plot for Time to First Dermatologic Event: Safety population



Active Filter Summary

	Obs	Subjects
ADSL	254/254	254/254
ADTTE	254/254	254/254

Active Filter Variables

ADSL

ADTTE

Add Filter Variables

Add `ADSL` filter

Select variable to filter

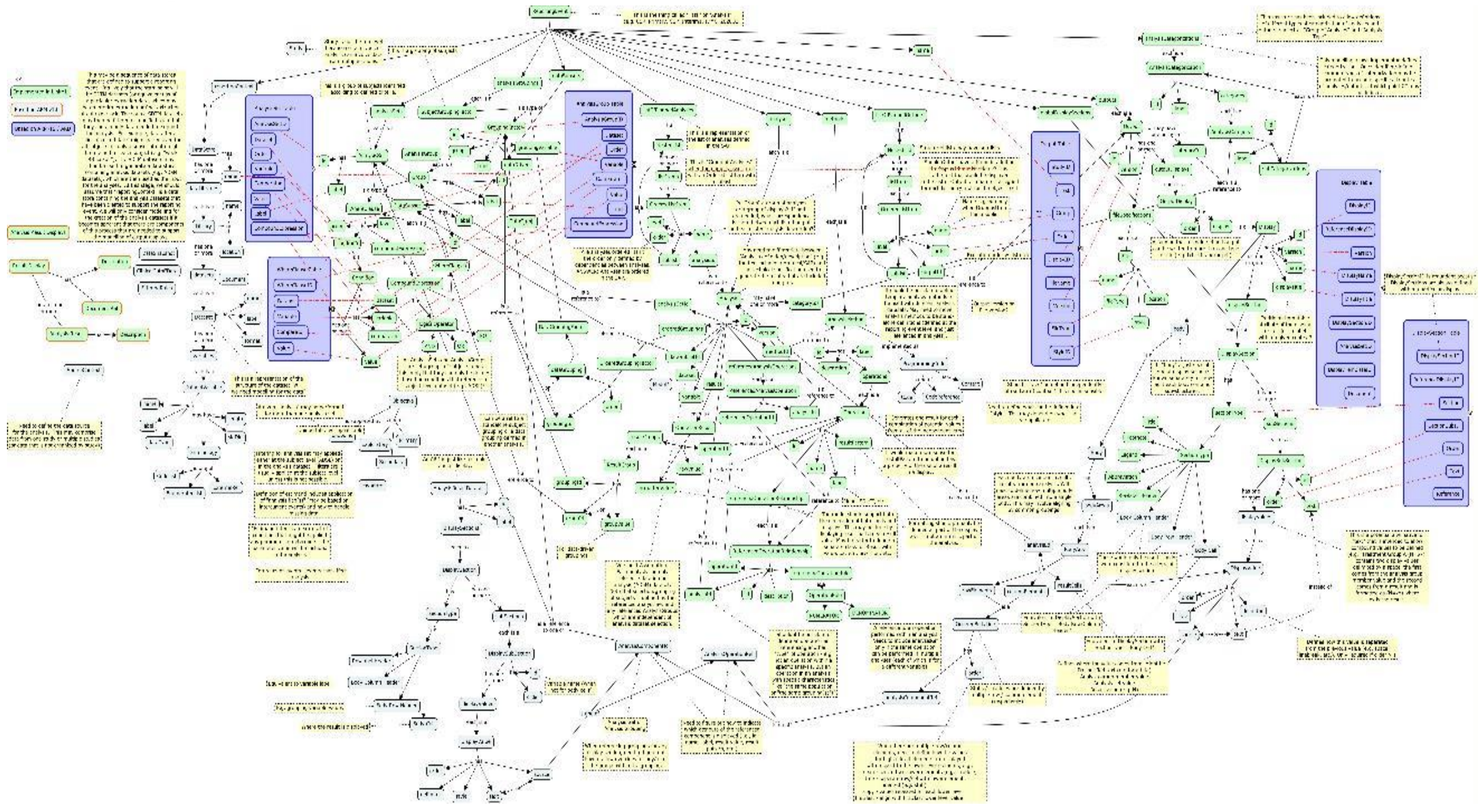
Add `ADTTE` filter

Select variable to filter

CDISC Initiatives at Glance
Standards for 2041 Vision

Analysis Results Standards

Conceptual Model



- Use analysis results metadata to drive the **automation of results**
- Support **storage**, access, **processing** and **reproducibility** of results
- Improved **navigation** and **reusability** of analyses and results
- **Traceability** to Protocol/SAP and to input ADaM data

With permission from Peter Van Reusel, Chief Standards Officer, CDISC

CDISC Initiatives at Glance
Standards for 2041 Vision

Thanks and Goodbye SAS XPT
Welcome Dataset-JSON

CLINICAL LEADER

Guest Column | July 12, 2023

No More XPT? Piloting New Dataset-JSON For FDA Submissions

By Sam Hume, D.Sc., vice president, data science, CDISC

When submitting study datasets, the FDA requires organizations to use the SAS V5 XPORT (XPT), a format that dates back to 1989. Originally announced in the FDA's 1999 *Guidance for Industry – Providing Regulatory Submissions in Electronic Format; General Considerations*, the XPT requirement set the format for representing datasets in the CDISC Foundational Standards. Since then, many aspects of the submission process have improved, yet the XPT requirement has remained. The outdated XPT format imposes restrictions on submission data, including limited data types, no Unicode support, variable name and field size constraints, inefficient use of storage space, lack of extensibility, and insufficient metadata. Moreover, XPT's binary format limits its utility for use in many modern data exchange scenarios.

CDISC developed Dataset-JSON, a new dataset exchange format, to replace XPT. Working with the FDA and industry participants, CDISC and PHUSE lead a new pilot project to test Dataset-JSON for use in regulatory submissions as well as other dataset exchange

CDISC Initiatives at Glance
Standards for 2041 Vision

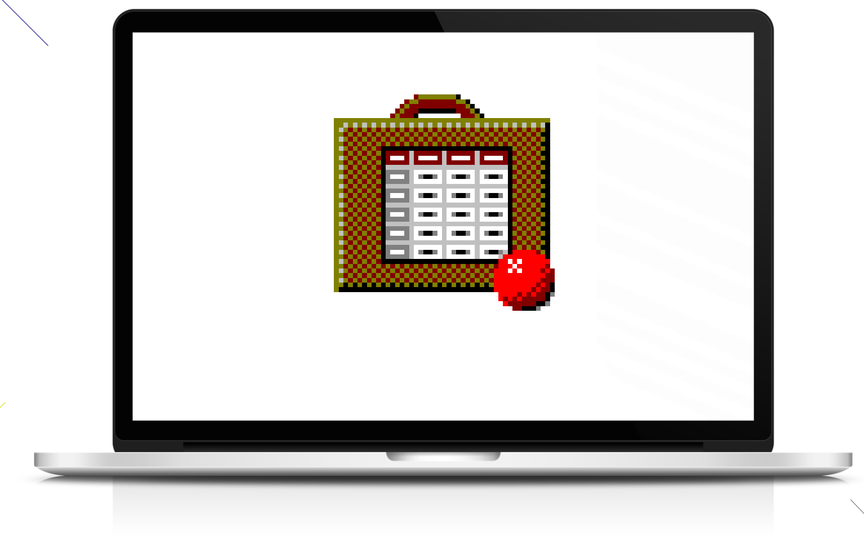
Thanks, and Goodbye SAS XPT
Welcome Dataset-JSON

Regulatory

Currently Mandated by Regulatory Agencies

Pre-history

Considered outdated and antiquated



Limitations of XPT v5

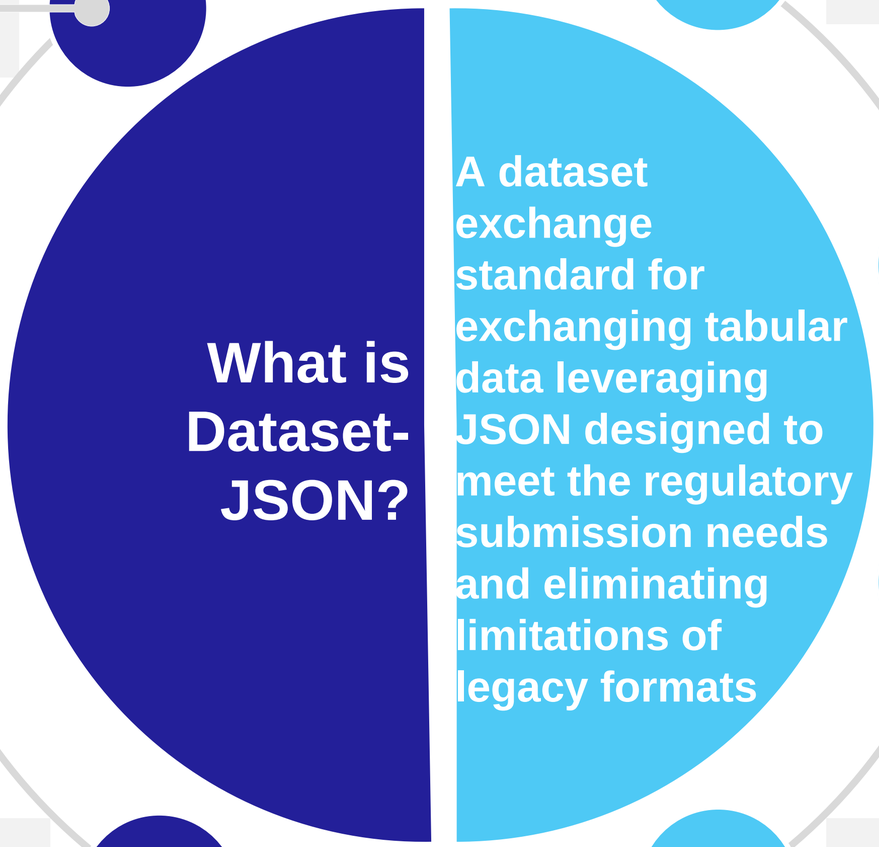
- Numeric limitations, antiquated format
- Stores data in its own numeric way
- Character limitations, no UTF-8 encoding
- No support for characters from other languages
- String & Column limitations (variable names > 8, labels > 40, data > 200)
- No metadata extensibility

No more public complaints..

….from my friend Jozef Aertz

CDISC Initiatives at Glance
Standards for 2041 Vision

Thanks and Goodbye SAS XPT
Welcome Dataset-JSON

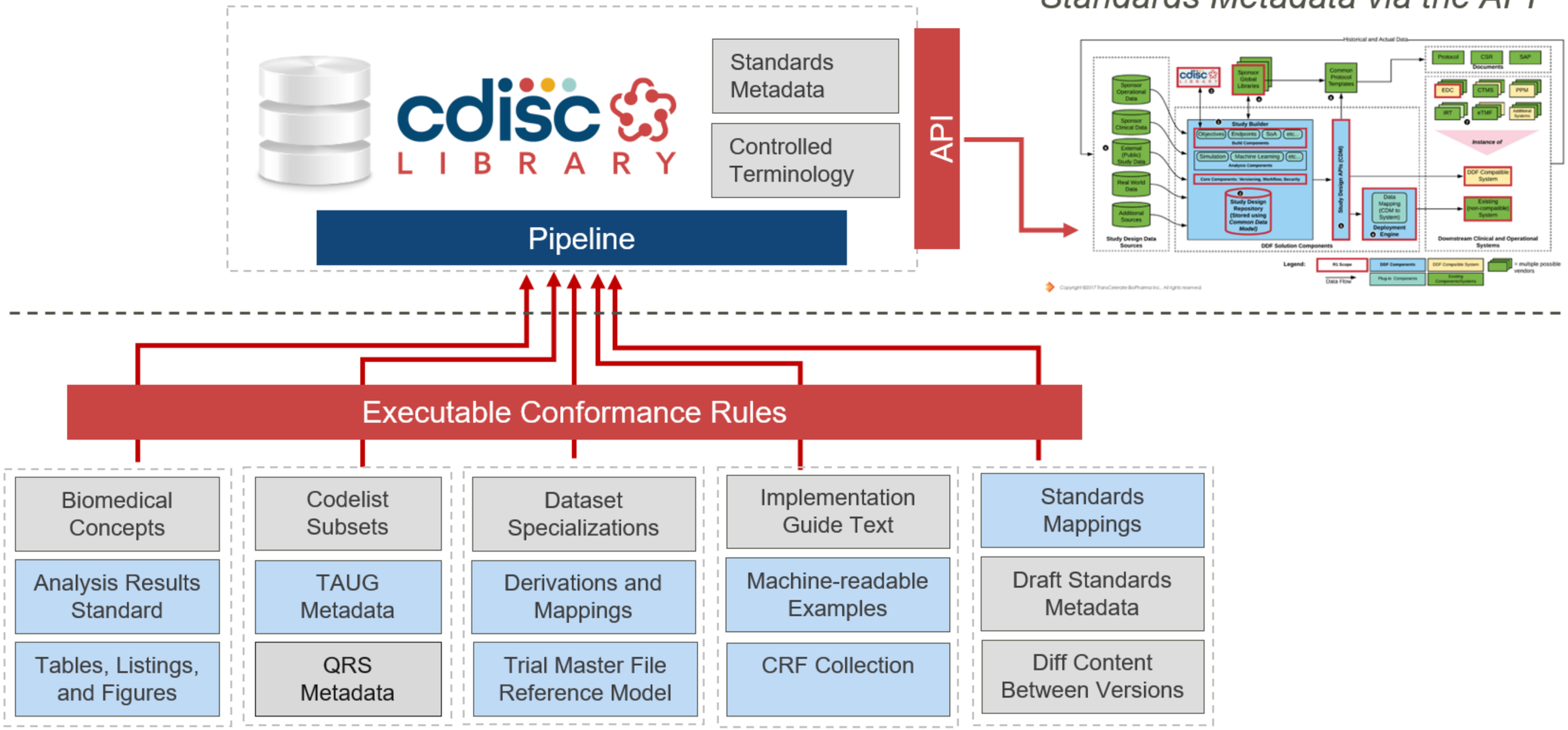


- Based on the JSON standard used worldwide
- Remove variable naming, width, or format limitations
- Open-source and truly human readable
- Simple transformation to/from SAS data
- Same or smaller file sizes relative to current required format
- Pilot

CDISC Initiatives at Glance
Standards for 2041 Vision

Standards as a Service

Software Applications Consume Standards Metadata via the API



With permission from Peter Van Reusel, Chief Standards Officer, CDISC

Open-Source for 2041 Vision

Supports and promotes open-source software projects that create tools for implementing or developing CDISC standards to drive innovation in the CDISC community

With permission from Peter Van Reusel, Chief Standards Officer, CDISC

Open-Source for 2041 Vision

Open-Source for 2041 Vision

Open-Source for 2041 Vision

Open-Source for 2041 Vision

Final Remarks
What is there for you?

We have one fundamental advantage over our peers, 5 years ago we invested heavily in a data lake called, we're leveraging that data lake to move AI very quickly in the company

Vasant Narasimhan

Follow the (R)evolution

Continuous Development

Adapt

Don't be afraid

We will survive AI

Useful Resources

- “Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document”, FDA Guidance for the Industry
- “Integration Strategies in Support of ISS/ISE Submissions” – PHUSE White Paper 2020, https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/Integration+Strategies+in+Support+of+ISS+ISE+Submissions.pdf
- “ADaM Structures for Integration: A Preview”, W. Zhong, K. Minkalis and D. Bauer, PharmaSUG 2018

- “ADaMIG v1.2 & ADaM Integration”, CDISC Webinar, 2019, https://www.cdisc.org/events/webinar/adamig-v1-2-adam-integration
- “Expert Answers to Community Questions” PHUSE webinar Friday March 26th, 2021 https://event.on24.com/eventRegistration/EventLobbyServlet?target=reg20.jsp&referrer=&eventid=3023348&sessionid=1&key=15BC66BD7480E5D87BBC2202C798E76C&regTag=&V2=false&sourcepage=register

- “Study Data Standardization Plan” https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/SDSP.zip
- “The PHUSE Recommendations for Pooled Submissions with WHODrug B3 Format Data White Paper”, https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/Recommendations+for+Pooled+Submissions+with+WHODrug+B3+Format+Data.pdf

Thank You

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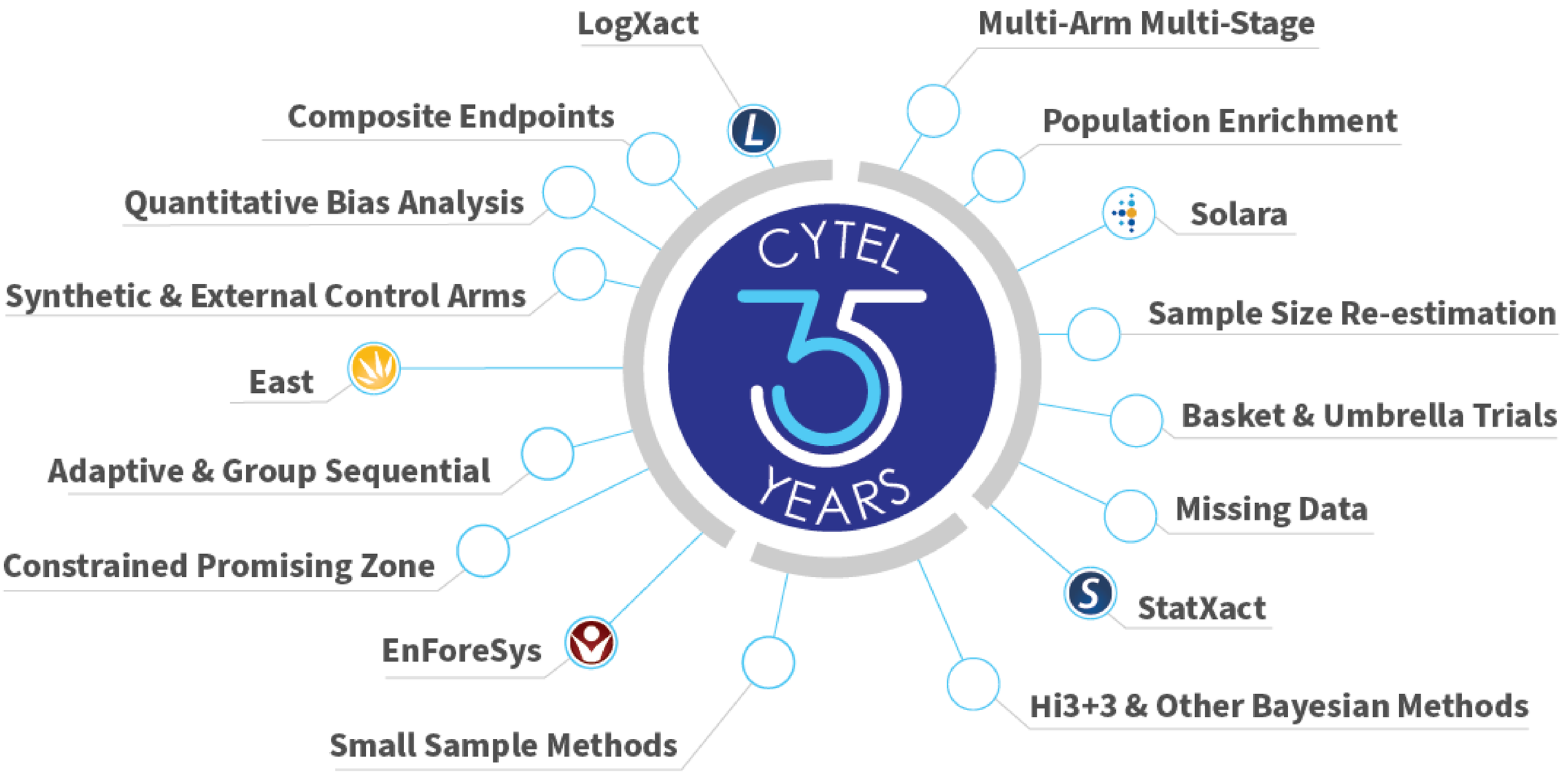
LogXact
Multi-Arm Multi-Stage
Composite Endpoints
Population Enrichment
Quantitative Bias Analysis
Solara
Synthetic & External Control Arms
Sample Size Re-estimation
East
Basket & Umbrella Trials
Adaptive & Group Sequential
Missing Data
Constrained Promising Zone
StatXact
EnForeSys
Hi3+3 & Other Bayesian Methods
Small Sample Methods
CYTEL
35
YEARS

Abstract

In recent years, the **emergence of data standards has significantly accelerated the review process and fostered a sense of common understanding** within the pharmaceutical community, now speaking the same language. These standards have also facilitated **better communication with regulatory agencies worldwide**. This remarkable transformation owes its success to organizations like **CDISC** and the support of numerous volunteers from diverse organizations across the globe.

As we progress further, **a new revolution is underway**, driven by the proliferation of **open-source initiatives**. This movement brings together volunteers from various organizations, united in their collaborative efforts to develop and maintain open-source tools. This, combined with the effective utilization of data standards, plays a crucial role in harnessing automation within our industry.

Through this presentation, I aim **to explore these pioneering initiatives and evolving standards, providing a glimpse into the future of data submission**.

Backup Slides

Timeline

2020
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2021
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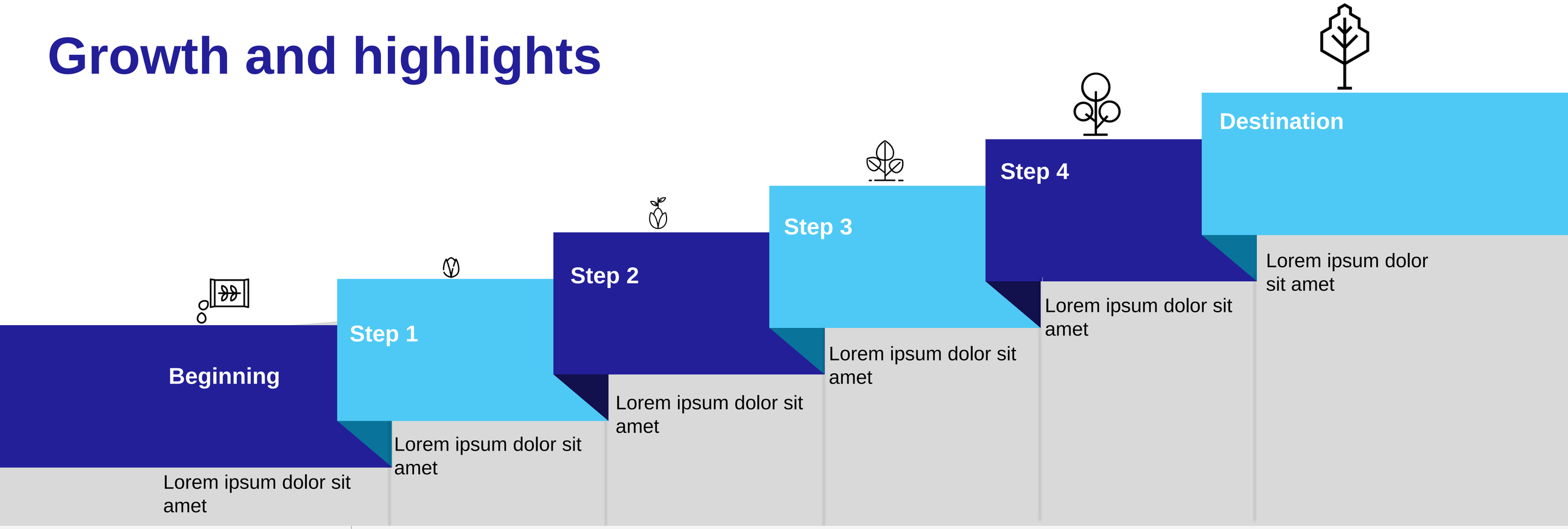
Growth and highlights



Highlights

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Four parts with laptop

Title

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