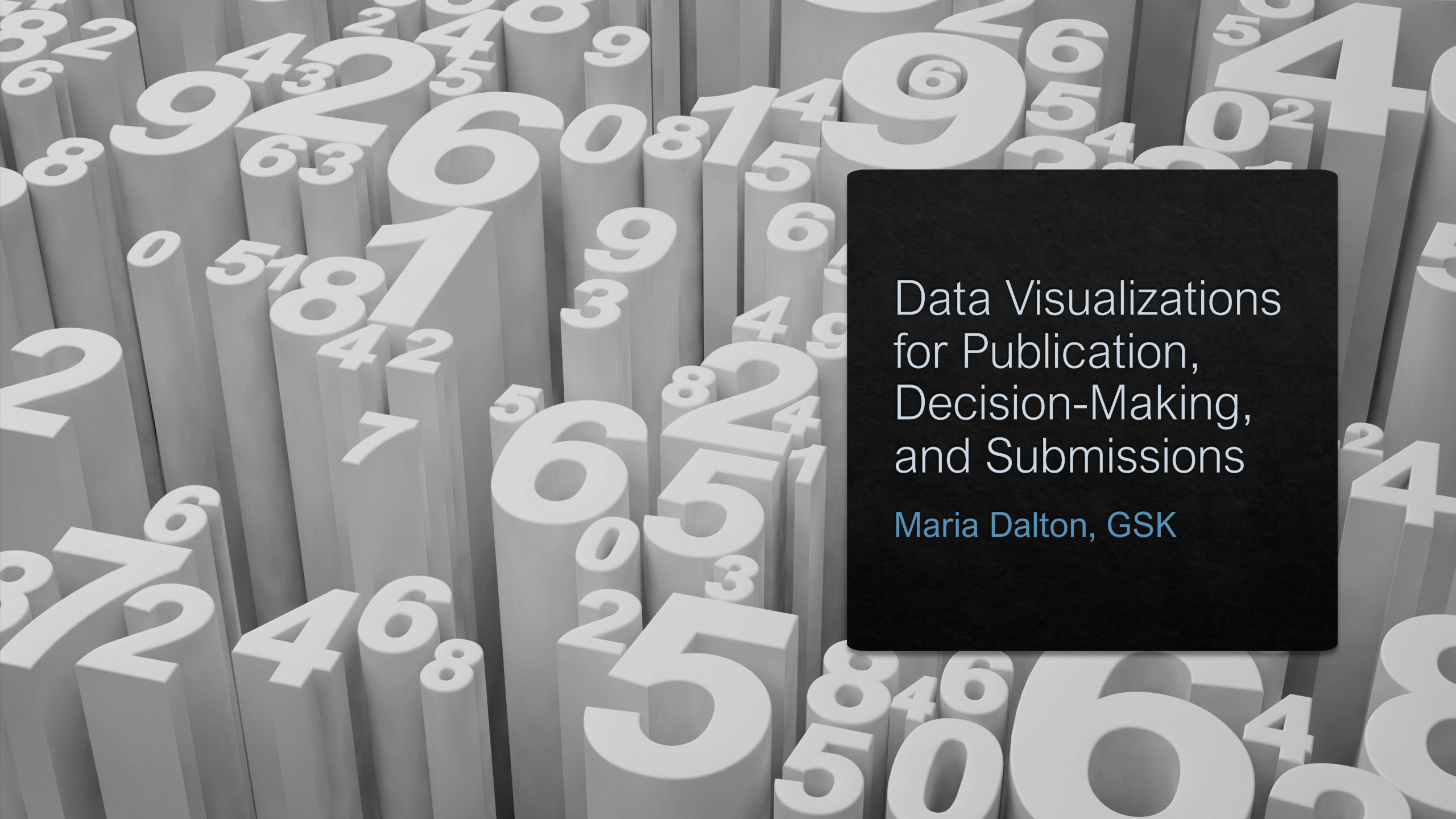


The background of the slide is a dense, grayscale field of three-dimensional numbers. The numbers, ranging from 0 to 9, are rendered in a bold, sans-serif font and are oriented at various angles, creating a sense of depth and movement. They appear to be floating or stacked, with some numbers in the foreground being larger and more prominent than others in the background.

Data Visualizations for Publication, Decision-Making, and Submissions

Maria Dalton, GSK

Scope of Presentation

- ❑ Web-based interactive data visualization applications
 - Filtering/subsetting
 - Drill-down capability (click on or lasso data points)
 - Interactive Patient Profiles
- ❑ Clinical CDISC data (SDTM and ADaM)

- ❑ Platforms
 - Commercial Off-the-Shelf products
 - R/Shiny apps
- ❑ Not Covered
 - R or Shiny programming
 - Graphics

Audience:

Anyone interested in expanding the vision & usage of interactive data visualizations

Interactive Data Visualizations in Biopharma



Interactive Analysis for Decision Making & Submissions

- An update from PHUSE Data Visualization Project



> [Ther Innov Regul Sci](#). 2018 Nov;52(6):696-700. doi: 10.1177/2168479018754846. Epub 2018 Feb 5.

The Safety Explorer Suite: Interactive Safety Monitoring for Clinical Trials

Jeremy Wildfire¹, Ryan Bailey¹, Rebecca Z Krouse¹, Spencer Childress¹, Britt Sikora¹, Nathan Bryant¹, Shane Rosanbalm¹, Emily Wilson¹, Jack G Modell¹



Project RAPIDO

Transforming our analyses

Realtime Clinical Summaries

Data from CDISC SDTM/ADaM Pilot Project: Lilly Study H2Q-MC-LZZT(c) in Alzheimer's Disease

Interactive Data Visualizations in Biopharma



Benefits

- Quick insights – don't have to wait for programmer to produce and QC a new display
- Data Democratization
- Reduce number of unused outputs for CSRs – eliminate “just-in-case analyses”
- Can reduce cycle time and improve efficiency

Main Uses In Biopharma Industry

- Data Exploration
- Instream data review
- Risk-based monitoring and Medical review
- Safety Review Boards
- Data Monitoring Committees
- Online data review tools to replace listings

Common Usage: Data Exploration



Common Warning: All outputs from this application are unvalidated. For validated outputs, please contact the study statistician and programmer.

In general: If results from interactive data exploration included in publications or submissions, they are reprogrammed & validated in Statistical Computing Environment (SCE)

- Results for publication and submission should be produced within a validated environment
- Follows Quality Control/validation SOP
- SCE creates audit trail and logs of all work
- Link between SCE and Publishing system

Data Visualizations for Publishing, Decision-Making and Submissions



Vision: Incorporate interactive data visualization directly into Good Clinical Practice-governed processes such as:

- Writing Clinical Study Reports & publications
- Decision-making
- Inclusion in submission packages to regulatory agencies



GSK RAPIDO Data Viewer

Vision

- Allow non-Biostatisticians to explore clinical data interactively using ADaM datasets as input
- Improve efficiency / cycle times for CSRs & submissions
- Generate validated reports for publications and submissions

Design

- Validated Enterprise Software with audit trail and access control
- Bespoke R / Shiny app with React, Hosted on Azure cloud, Data access with Azure Synapse
- Integrated into Statistical Computing Environment with direct link to data pipeline & regular data refreshes
- Compliant with Results Dissemination, Data Reuse, Disclosure, Informed Consent, Privacy requirements
- User-Friendly Data Exploration and Collaboration Features
 - Controlled capability to create new displays (e.g., drag and drop cross-tabs, add new subgroup variables)
 - Bookmark displays for sharing, Store user settings, favorites, and patient subsets across different sessions
 - Drill-down into displays to see subject details
- Library of validated R packages that can be reused in SCE or other Shiny apps

Considerations and Challenges

- ❑ Enterprise software with Access Control and Security
- ❑ Computer system validation, including R validation
- ❑ Compliance with disclosure and Human Subject research requirements
- ❑ Statistical inference in interactive displays
- ❑ Standardization Challenges
 - ADaM variability
 - Standardizing analyses and derivations
- ❑ New skills and responsibilities

Enterprise Software



Cloud-based
Scalable
Architecture



New technologies
(Azure Cloud, Azure
Synapse)



Integration with
Statistical Computing
Environment



Agile software
development and
project
management



Library of validated R
packages that can be
reused in SCE or other
Shiny apps



Access control and
security

Computer System Validation

From FDA Glossary of Computer System Software Development Terminology:

validation. (1) (FDA) Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. Contrast with data validation.

Requirements

- Regulatory agencies require that computer systems used in clinical trials (including statistical analysis) be validated with appropriate software testing procedures to demonstrate they are reliable
- Validation must be documented.
- Additional requirements: security safeguards, audit trails, date/time stamps, Standard Operation Procedures (SOPs), controls for system changes, and training of personnel.

Computer System Validation

Key Steps in Computer System Validation

- User requirement specifications
- Functional requirement specifications
- Validation Plan and Risk assessment
- Unit Testing
- Systems Integration Testing
- User Acceptance Testing
- Validation Traceability Matrix
- Network and Infrastructure Qualification

Take Home Messages

- Documentation is key
- Essential to have IT and Computer System Quality Assurance expertise
- Allocate plenty of time and resource

R Validation



R Consortium Working Groups for R Validation and Use of R for Regulatory Submissions

- [R Validation Hub \(Pharmar\)](#): a cross-industry initiative whose mission is to enable the use of R by the Bio-Pharmaceutical Industry in a regulatory setting, where the output may be used in submissions to regulatory agencies.
- [R Tables for Regulatory Submission \(RTRS\)](#): Develop standards for creating tables that meet the requirements of FDA submission documents
- [Submissions](#): Focus on IT and platform challenges that must be addressed in order to make “all R” regulatory submissions.

White Papers

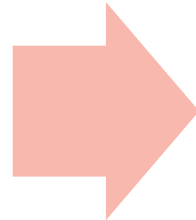
- [R: Regulatory Compliance and Validation Issues A Guidance Document for the Use of R in Regulated Clinical Trial Environments](#)
- [A Risk-Based Approach for Assessing R Package Accuracy within a Validated Environment](#):

Human Subject Research Requirements



Requirements

- Validated systems
- Security and Access Control
- Informed Consent
- GDPR / Privacy
 - e.g., if subject requests erasure of data under GDPR
- Disclose results that provide important scientific knowledge or are relevant for patient care



Process Controls

- Processes
 - New Work Instruction
 - Updates to existing SOPs, such as Quality Control and CSR writing
- Terms and Conditions
 - Users must agree to Terms and Conditions in required training and on sign-on screen

System Controls

- Validated with security, access control, audit trail
- Data pipeline controls
 - Restrict data extraction
- Bookmark displays that require disclosure
- Track data reuse after CSR
- Ability to change to anonymized data if required
- Controls and guidance on use of statistical inference

Statistical Inference



Interactive data visualization tools allow for data exploration that is not fully prespecified in protocol and analysis plan - Can lead to “data-driven analysis decisions”

- Fishing for publishable p -values, i.e., *p-hacking*
- New subgroup analyses:
“You should always do subgroup analysis and never believe the results.” – Sir Richard Peto
- Small sample size could lead to violation of the normality assumption

Reference: <https://www.tandfonline.com/doi/full/10.1080/00031305.2018.1518264>

Standardization Challenges

Goals

- Standard set of visualizations and analyses across all studies (TA-specific standards as well)
- Code that works correctly across all ADaM datasets at GSK
- Consistent interface across various interactive data visualization tools at GSK
- Improve efficiency – reduce resource needed for CSRs and submissions
- Decrease cycle times

Challenges

- Variability of input ADaM datasets
- Agreement on standard visualizations and analyses
- Allow study-level customizations
- Several different interactive data visualization tools used at GSK



New Skills Needed



Software
development

User Interface
design

Computer
System
validation

Agile software
development &
project mgmt

R and Shiny
coding

Data
visualization /
graphics

Trailblazers



PHUSE Best Practices for Interactive Analyses for Decision Making and Submission

- Pilot 1: eSub with embedded interactive data displays (Eli Lilly - Mary Nilsson, Zachary Skrivanek)
- Pilot 2: Docker POC with R/Shiny-based interactive tool (Genentech - Nilesh Narayan, Doug Kelkhoff, Xiangyun Wang)
- 2020 PHUSE US Connect Presentation: https://www.lexjansen.com/phuse-us/2020/dv/DV13_ppt.pdf
- White paper coming soon!

bioWARP from Roche Diagnostics

- “bioWARP (biostatistical Web-Applications and R Procedures) is a Shiny application enabling employees at Roche Diagnostics to create validated reports for regulatory authorities’ submissions.”
- R/Pharma 2018: [R/Pharma 2018 \(rinpharma.github.io\)](https://rinpharma.github.io), PSI Web 2019: [PowerPoint Presentation](#)

Accumulus Synergy (<https://www.accumulus.org/>)

- Goal: Global Cloud-based Data Sharing Platform between Biopharmaceutical industry & health authorities
- Formed in 2020 with 10 leading Biopharma companies

Thank You



Questions, Discussion, Feedback are Welcome

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