

Review and Analysis of SEND Standardized Data at the FDA

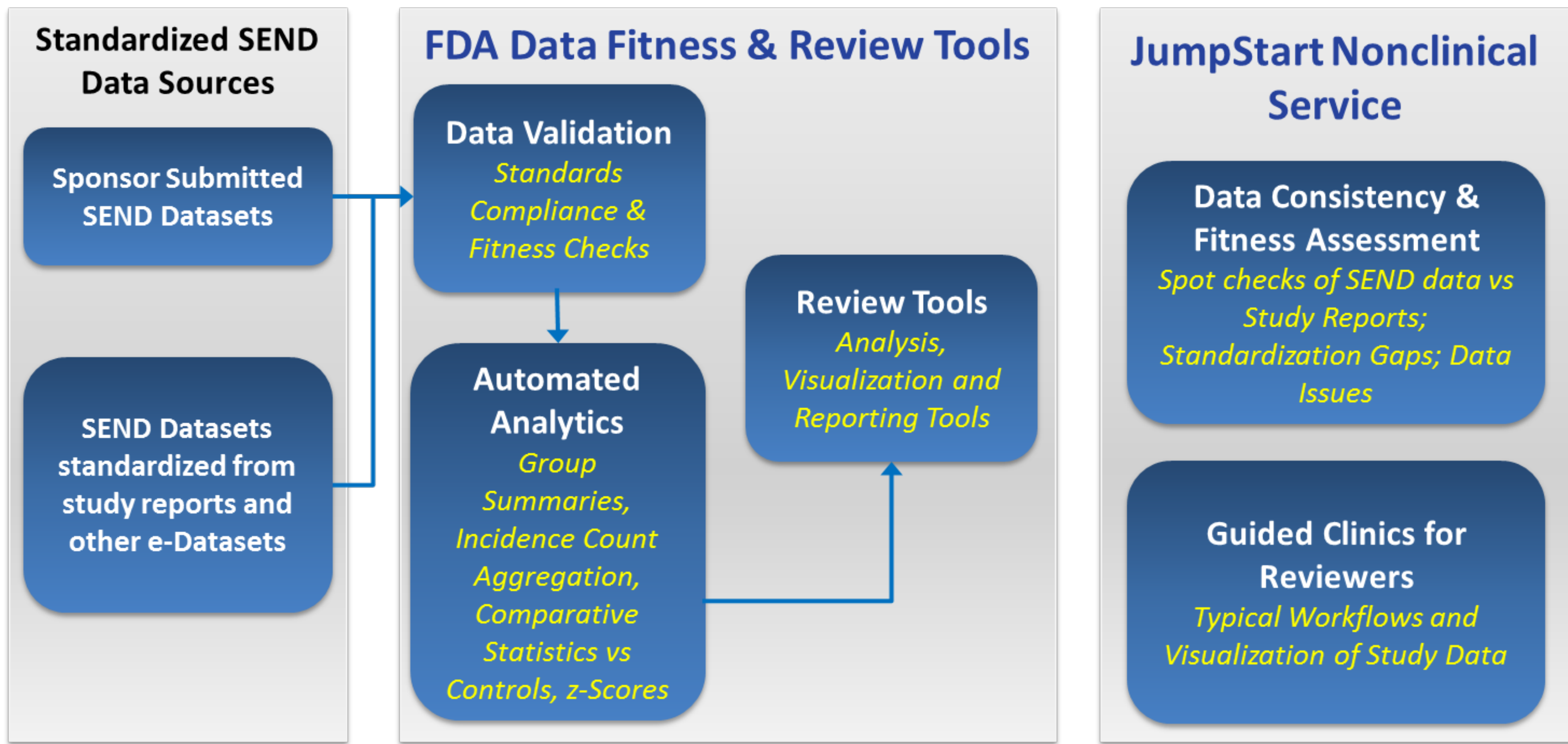
Kristi Johnson, Jillian Sanford, Karen Porter, Jon Kimball and Shree Nath

PointCross Life Sciences Inc., 1010 Wayne Avenue, Suite 860, Silver Spring, MD 20910, USA; email: kristi@pointcross.com

1 - Summary

The FDA JumpStart program prepares submitted standardized data for nonclinical and clinical trials into a form that serves the needs of reviewers significantly improving the review process. Jumpstart has been focused on manual preparation of CDISC STDM clinical data for review purposes. SEND standardized nonclinical data will soon need to be submitted in compliance with the recent FDA guidance. In preparation, the FDA has standardized nonclinical study data extracted from sponsor study reports for use by reviewers.

At the FDA, SEND datasets are subjected to **automated data fitness checks** and creation of **analysis views** for reviewers. These include **histopathology data visualization**, **clinical pathology** trends and controls to combine treatment groups and exclude subjects without manual intervention. JumpStart clinics that include data consistency and fitness assessments, and walkthroughs of analytic views and visualizations are provided to reviewers. Valuable feedback to improve review tools and the JumpStart program have been gathered from reviewers.



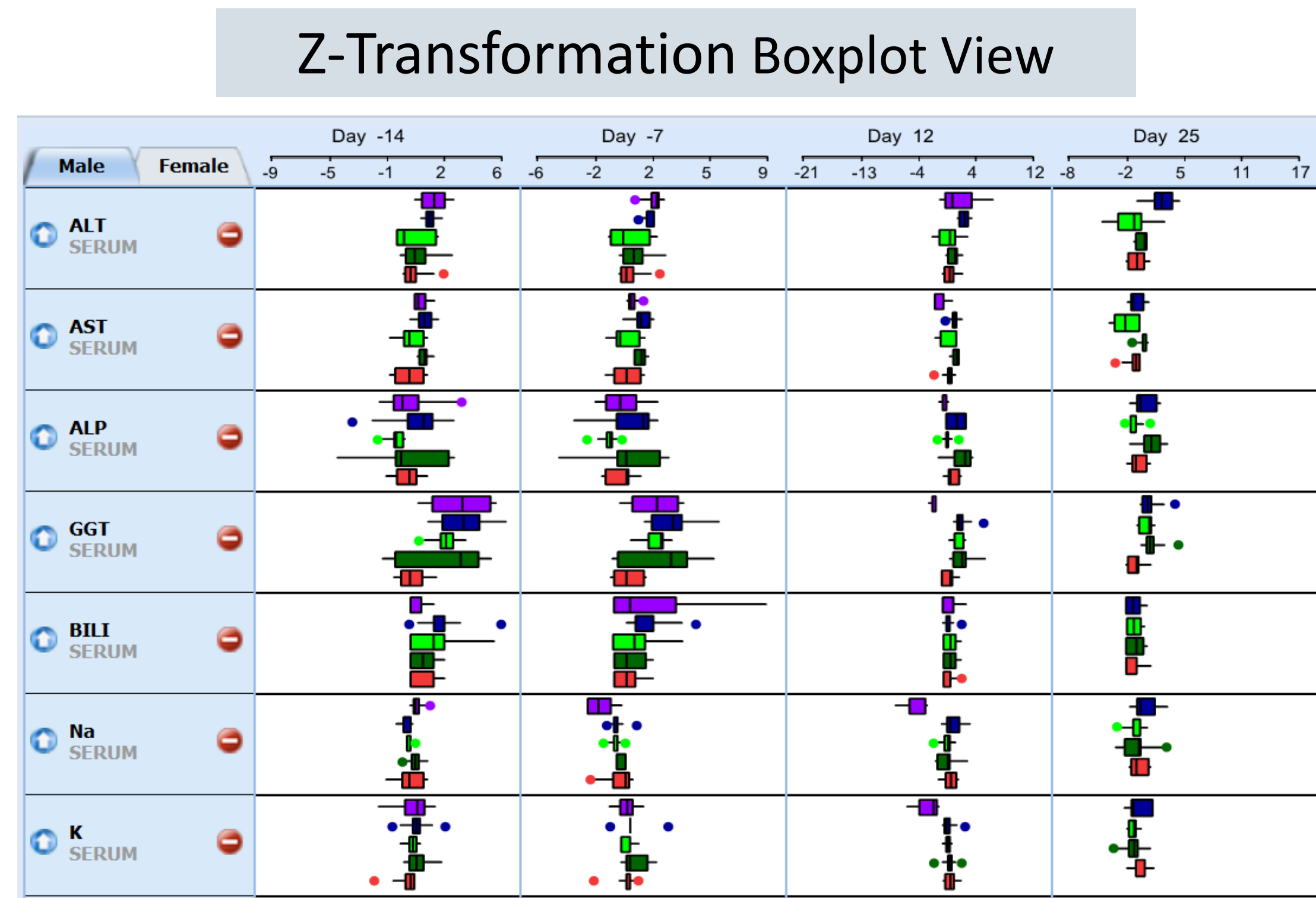
3 – Data Analysis and Visualization

The typical study data review clinic consists of:

- Data consistency and standardization assessments
- Trial design overview and export of **trial summary** data for use in reports
- Graphical timeline views of **planned protocol** events and measurements
- Views of **Demographics** and **Exposure** domains
- Tabular and Graphical views of **quantitative** and **qualitative** findings data
- Trend comparison across **time**, **dosing groups** and **measurements**
- Consolidated views of **Histopathology** findings

Reviews of sponsor submitted data may include:

- **Clubbing of trial sets** to reflect sponsor defined dosing groups – this allows reviewers to re-create group summaries in the PDF reports and compare their analyses to the sponsor reported summaries. It also allows reviewers to combine groups as they see fit to perform independent data reviews.
- Use of **subject-level exclusion flags** to re-analyze study data
- Detailed review of **all findings** for a single subject
- Assessment of any signals in other studies included in the sponsor submission



Histopathology Consolidated View											
Legend Key: Relative Incidence											
1: 0-20% 2: 21-40% 3: 41-60% 4: 61-80% 5: 81-100%											
Color Gradient Off											
M											
F											
Findings											
Modifiers											
Severity											
1: GROUP 1 2: GROUP 2 3: GROUP 3 4: GROUP 4 5: GROUP 5 6: GROUP 6 7: GROUP 7 8: GROUP 8 9: GROUP 9 10: GROUP 10 11: GROUP 11 12: GROUP 12											
#Examined											
HISTOPATH											
Infiltration: mononuclear cell											
Total											
#Examined											
HISTOPATH											
Dilatation: tubular lamina											
Total											
Fibrosis/atrophy											
Total											
#Examined											
HISTOPATH											
Infiltration: mononuclear cell											
Total											
#Examined											
HISTOPATH											
Hyperplasia											
Total											
#Examined											
HISTOPATH											
Necrosis: tubular: single cell											
Total											
#Examined											
HISTOPATH											
Vacuolation: tubular: epithelium											
Total											
#Examined											
HISTOPATH											
Vacuolation: tubular: epithelium											
Total											

5 – Reviewer Feedback and Future Capabilities

In our interactions with reviewers, they have been positive about the use of standardized SEND data, and the supporting JumpStart processes and tools. The ability to directly work with digital study data, to access a range of automatically prepared graphical and tabular views, and use analysis outputs in reviewer reports are some of the key benefits that have been identified.

Valuable feedback has been gathered to further advance review capabilities such as **interactive graphical objects**, **cross-domain** views and **comparisons across studies**, and export of tabular and graphical reports into reviewer reports.

2 – Data Consistency and Fitness Issues

Several data issues have surfaced during our SEND standardization initiatives (with the FDA and Sponsors) and during preparations for JumpStart clinics. These include:

- **Data Consistency** gaps between SEND data and the corresponding study reports
- **Quality** issues including data representation choices that impact study reviews
- **Standards Compliance** issues; and
- Study **Data Collection or Reporting** gaps

Our experience suggests that these kinds of issues may require reviewers to spend significant time assessing both the SEND datasets and associated reports. They may also need to manually extract sponsor submitted data to prepare their reports when the SEND datasets are insufficient.

Further, consultation with sponsors may be needed. These challenges will delay the review process and may require re-submission of datasets that may not meet data quality expectations.

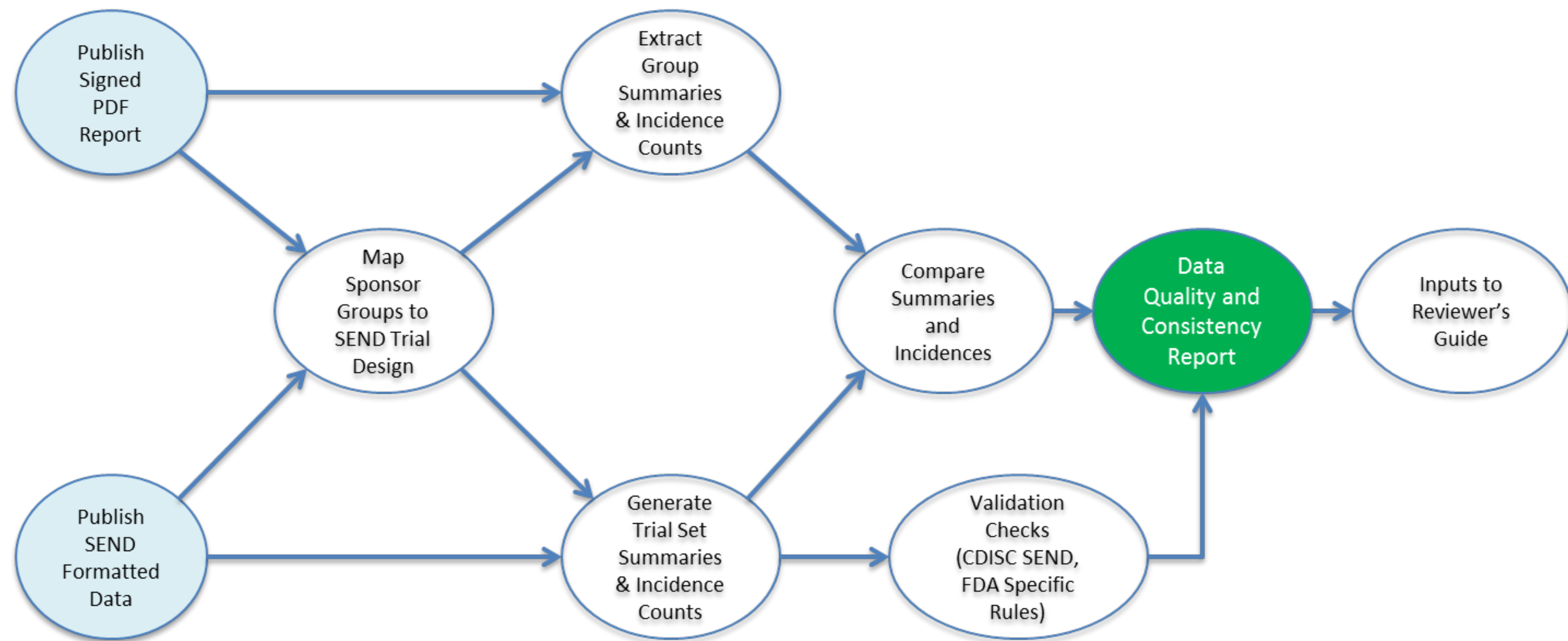
Standardized Data: Issues & Observations	Examples	Impacts
Inconsistencies in Trial Descriptions	Labels suggest only one gender in the study although design included both genders	Additional effort for reviewers to understand the design
Inconsistencies in Dosing Regimen	Dosing details in the PDF report and SEND datasets are different (e.g., ONCE vs Once Daily)	Reviewers need to spend time finding the right dosing details prior to data review
Incorrect definition of Pathology Results	Findings and severities incorrectly reported as modifiers (e.g., findings are noted as “both sides”)	Significant effort for reviewers to manually prepare histopath consolidated views for their reports
Differences in values between the SEND Data and PDF Reports	Body weight data in the SEND dataset does not match values for the same subject and time point in the PDF Report	Delays to the review process; may require sponsor clarification
Undefined codes in the SEND dataset	Wrong SEND representation where quantitative data are mixed with unexplained codes (e.g., “CS” for Clotted Samples)	NIMS does not summarize the results for reviewers. Manual work is required to export the data and re-create summaries in Excel
Lack of Dates or Timing Variables for Clinical Pathology measurements	Only the experimental start date is provided.	Exact date of each measurement must be manually calculated from the experimental start date. This delays the review process.

4 – What Sponsors can do to get Ready for SEND Submissions and Assure Data Consistency and Quality

Sponsors can initiate **SEND Readiness** programs focusing on the following areas:

- ✓ Involve representatives from different business units to prepare their organization for standardized submissions in time for FDA mandated deadlines
- ✓ Making sure that their entire data supply chain, from CROs and internal labs to the point of submission, is streamlined and aligned with related processes for Study Report preparation, SEND dataset generation and eCTD submissions
- ✓ Becoming competent on **Standards Compliance**: *SEND Data Representation, Trial Design Modeling, Controlled Terminologies and Define.xml*
- ✓ Understand how FDA reviewers may use standardized SEND datasets as part of the regulatory review process
- ✓ Provide SEND submissions to the FDA prior to the mandated deadlines and request feedback on data consistency and fitness observations.

Sponsors and their CROs should also consider applying **quality assurance** and **audit** processes to ensure that their standardized datasets are consistent with tabulated data in the study reports, and that they meet quality and completeness needs for review by the FDA. For the near-term, this can be done by conducting group summary and incidence counts consistency checks between study reports and SEND datasets as shown below. In the longer-term, as SEND is increasingly adopted, a common data resource for both study reports and SEND datasets can be established. Organizations like PhUSE can contribute solutions to these kinds of challenges that CROs and sponsors will confront as they implement the SEND standard in response to the FDA's binding guidance of December 2014.



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Disclaimer

The views and opinions expressed in this poster presentation are those of the authors.