Better CDISC Compliance Techniques result in faster Breakthrough Therapies

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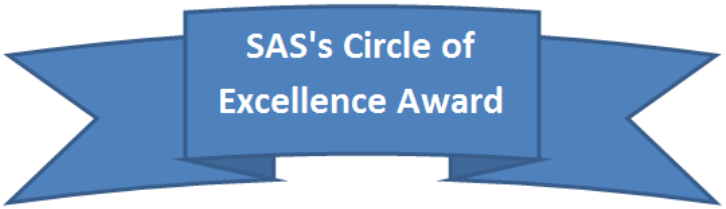


Breakthrough Therapies Impact Lives and Quality of Life

Phase III Clinical Trials can make a Big Impact

Amgen drug can help in early chemotherapy

Study shows Neulasta can reduce infection

By Allison Bruce
abruce@VenturaCountyStar.com

A recent study of Neulasta, a drug produced by Amgen Inc., could mean more doctors might consider the drug for their cancer patients at the earliest stages of chemotherapy.

The study, which came out in The Journal of Clinical Oncology, found that patients who were given Neulasta during their first cycle of chemotherapy and in subsequent cycles were more than 90 percent less likely to suffer from febrile neu-

Amgen is considering building a production plant in Switzerland. **D4**

tion than patients who are normally recommended for a drug such as Neulasta. But 17 percent of those taking a placebo developed febrile neutropenia, while only 1 percent of those taking Neulasta developed the condition.

"The high frequency of first-cycle febrile neutropenia in this study emphasizes the need to initiate Neulasta for the first cycle of chemotherapy to

Risks must be Monitored to assure Efficacy and Safety

FDA grows more cautious with drugs

By Linda A. Johnson
AP business writer

TRENTON, N.J. — Under growing scrutiny since the blockbuster painkiller Vioxx was pulled from the market, the Food and Drug Administration in recent months has rejected a slew of experimental drugs or delayed their approval and required more data.

Besides keeping drugs some patients might desperately need off the market, the rejections have battered drug company stock prices and are expected to increase the cost and time it takes to develop a new drug, not to mention the price of developing future ones.

Major companies affected

Denials and delays have hit everyone from pharmaceutical giants such as GlaxoSmithKline PLC, Merck & Co., Novartis AG, Sanofi-Aventis and Wyeth down to struggling startups trying to get their first drug on the market. The FDA also has stiffened warnings on several drugs, most prominently diabetes drugs Avandia and Actos, and five months ago made Novartis withdraw its constipation drug, Zelnorm.

"There have been no systematic changes in how we are approaching the approval standards for new applications," FDA spokesman Christopher Kelly said in an e-mail. "Whether the current public debate and criticism of FDA on drug safety has played any role in our actions is very hard to quantify."

But Chris Milne, associate director of the Tufts Center for the Study of Drug Development, said Friday the FDA has systematically implemented more controls for scrutinizing drugs, particularly for heart and liver side effects. While he thinks the trend on approvals is not yet clear, he said the FDA now is requiring experimental drugs similar to ones already on sale to be more effective and safer than their predecessors.

Some experts say they already see a trend toward increased rejections, although drugs for life-threatening diseases or conditions with no good current treatment are generally being approved.

"The FDA is being more cautious," analyst Steve Brozak of WBB Securities said, explaining that FDA staff now realize new drugs will be used by many patients beyond those intended — known as off-label use because the drug is taken for another condition than the one it was approved to treat. That often boosts the chances that some patients will be harmed by side effects.

He sees the FDA mentality now as: "It's got to be so safe that we're not going to be criticized ever" for approving a drug.

The agency has approved 61 percent of drug applications through mid-August, down from 73 percent in the same period last year, according to BioMedTracker, a biotech and pharmaceutical research service.

James Kumpel at Friedman, Billings, Ramsey & Co. just published a report showing FDA approvals of "new molecular entities" — drugs made from new chemical compounds rather than just twists on existing drugs — so far this year are at their lowest level in at least a decade.

Only seven were approved through the end of July, versus an average of 12 over the first seven months of each year since 1998.

"The FDA certainly has made it more difficult for pharmaceutical companies by pushing for more data and for more participants and for longer studies," said Kumpel, barriers he said will start limiting the number of new blockbusters.

Drug can cost $980 million

Already, the average cost of shepherding a potential drug from discovery through approval is $980 million, up from $802 million in 2000, and the process takes 14.2 years on average, according to Tufts.

"It appears that FDA has been on defense since 2004," Kumpel said.

That's when Merck withdrew its blockbuster painkiller Vioxx from the market because of increased risk of heart attacks and strokes, making Vioxx an instant poster child for drug safety issues.

Last April, the FDA rejected Merck's Arcoxia, a long-planned successor to Vioxx on sale in many other countries.

Just Friday, Endo Pharmaceuticals Holdings Inc. said the FDA for the second time asked for more time to review its approved migraine drug Frova for a new use, preventing menstrual migraines.

In between, the FDA has cited safety or effectiveness questions in rejecting or delaying approval for experimental drugs including Novartis' diabetes drug Galvus, Sanofi-Aventis' weight-loss drug Zimulti, and even a higher dose of GlaxoSmithKline's Advair Diskus for bronchitis and emphysema symptoms.

Likewise, small pharmaceutical companies have been hurt. One, Pozen Inc., this month got its second FDA request for more information about a migraine treatment called Trexima it is jointly developing with GlaxoSmithKline. That news sent Pozen shares down 46 percent.

Scott Gottlieb, an American Enterprise Institute fellow who was FDA deputy commissioner until January, said drug companies have long complained that FDA was too conservative. Now, there's even more uncertainty both at the agency and in the industry.

For drugs where benefits don't strongly outweigh risks, Gottlieb said, "The agency errs on the side of caution."

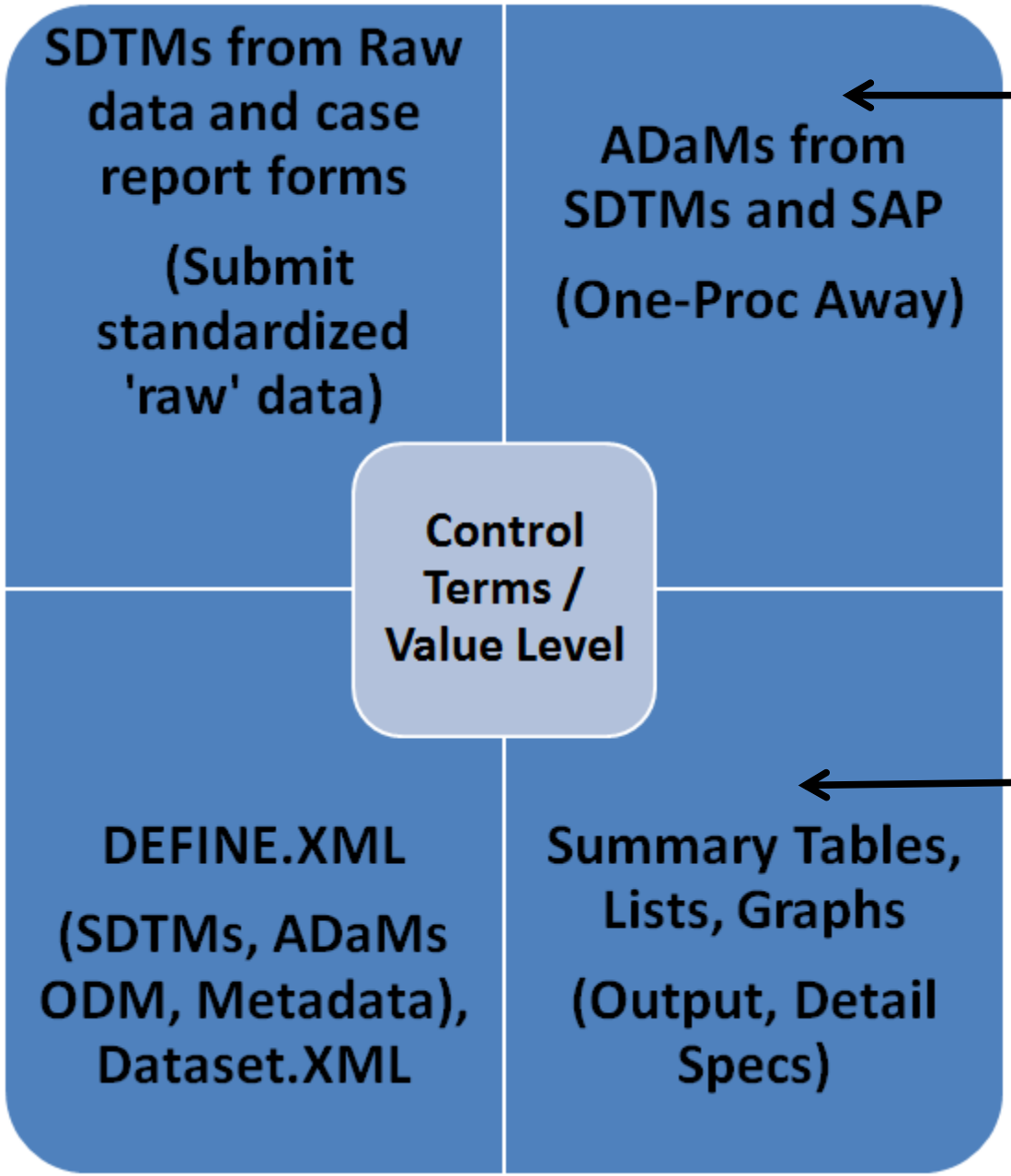
You *Can* Reach for the Stars

- ✓ Control and Confirm CDISC Compliance
- ✓ Use better SAS Programming Techniques and Technology
- ✓ Produce Efficacy results that significantly improve Patient Outcome
- ✓ Reduce Risks by monitoring adverse events
- ✓ Be motivated to overcome Data and Analysis Challenges

A World ***with*** CDISC Standards – ***Good*** for BOTH FDA and Sponsors

- ✓ **Meet customer expectations without any surprises**
- ✓ **FDA can start the review process without any initial questions or issues since submission meets requirements**

A World ***with*** CDISC Standards

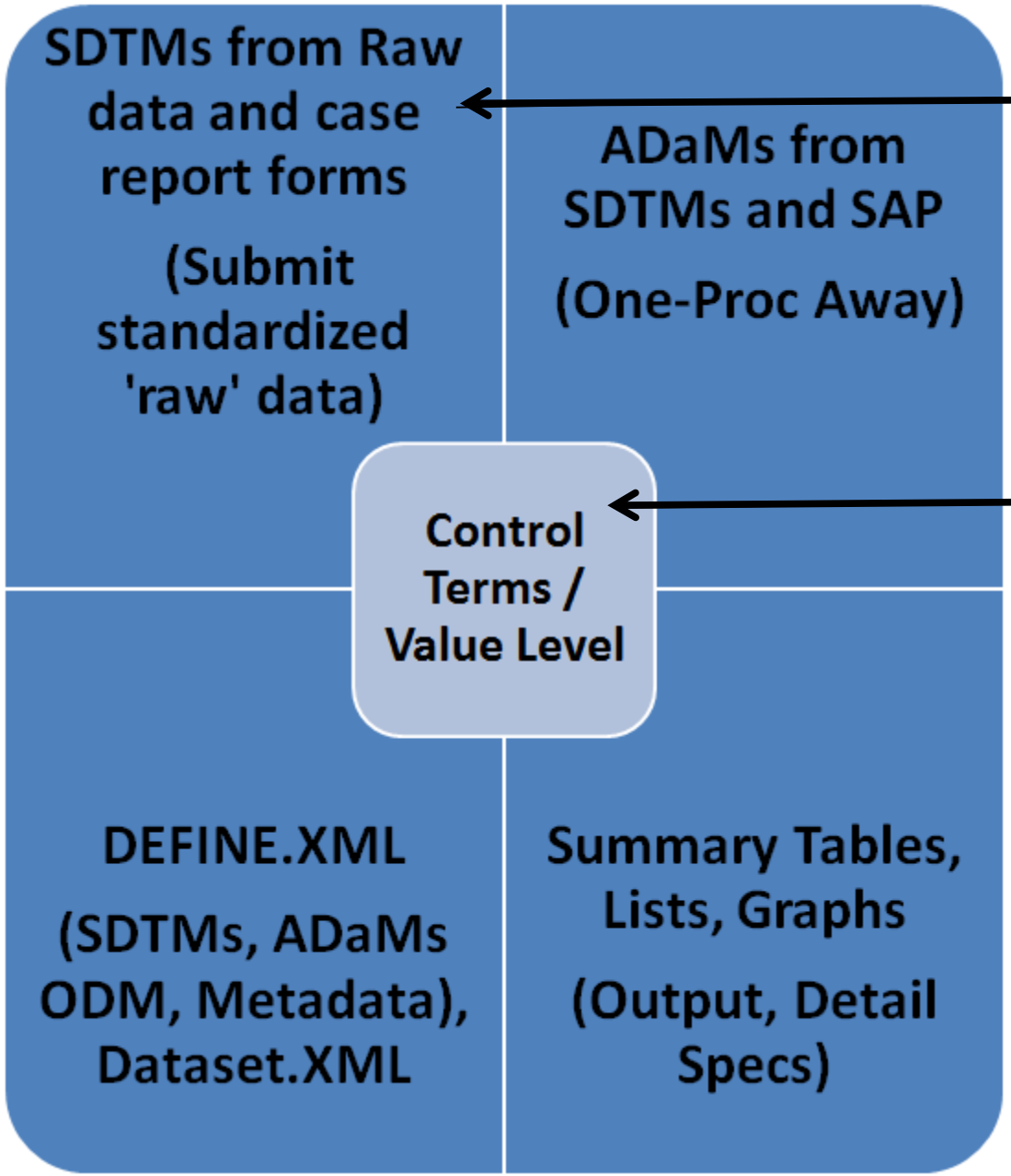


One-Proc Away ADaM gives power to query by subsetting, grouping and analyzing to answer questions

CDISC standards are based on FDA submission review experience

Specifications as metadata are useful to document, automate and assure higher FDA compliance

A World ***without*** CDISC Standards

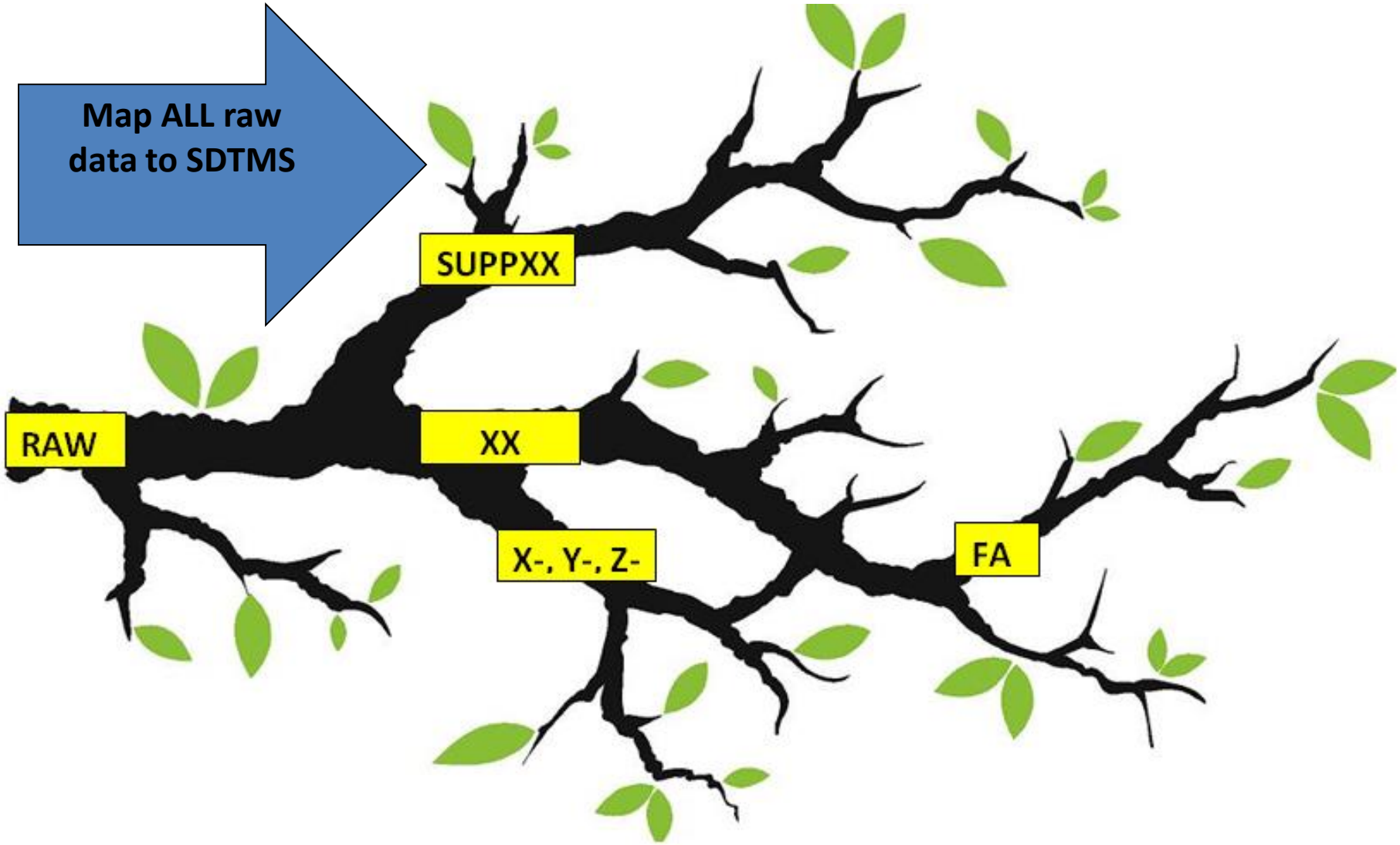


Issues with non-standard lab units when trying to combine and analyze data?

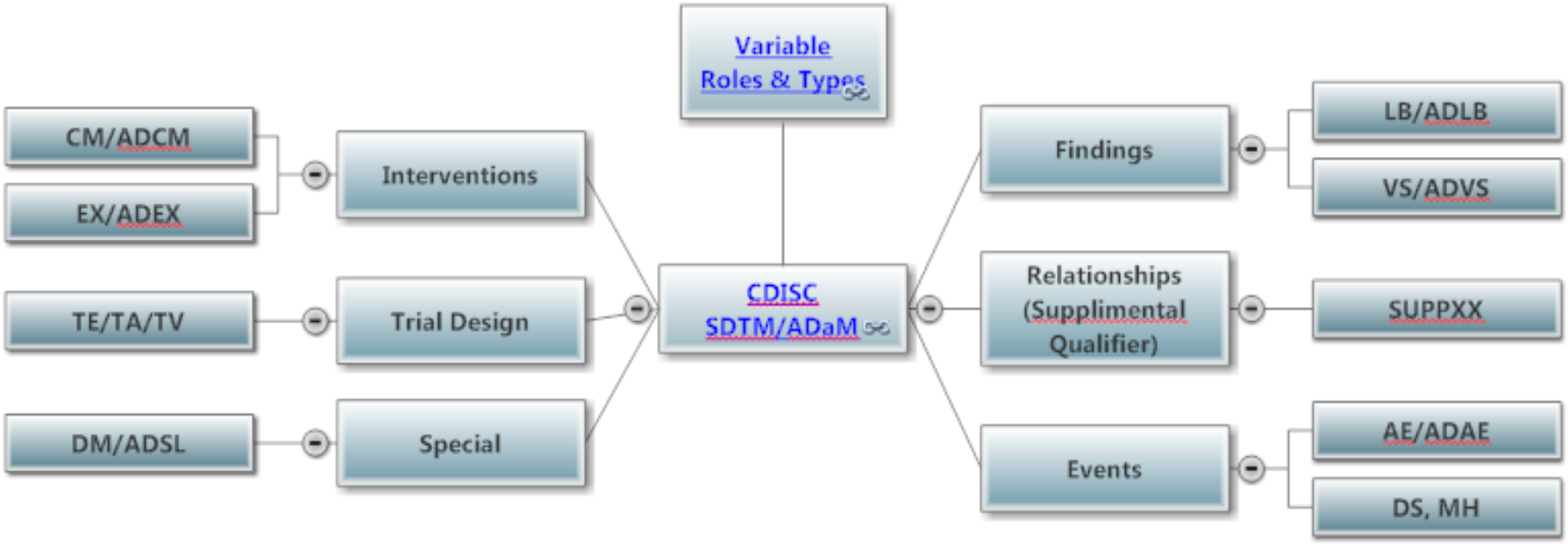
Issues with case sensitivity, special characters or spaces when trying to subset, group or summarize?

We all have experienced these issues

Channels for Mapping SDTMs allow for both Mapped and Unmapped data



SDTM and ADaM Domains Mindmap



1) 80% time to create SDTMs, 20% time to create ADaMs
2) Create ADaMs only based on SAP for Summary Tables
3) ADaMs may combine XX with SUPPXX
4) ADaMs may have derived records per USUBJID to facilitate 'One-Proc-Away' concept

SDTMs by Relationship to Patients

Other	Interventions	Events	Findings
Who are the patients?	***What do we give to patients?***	***What happens to patients?***	***What do we measure on a regular basis?***
(	**20%**	)	**80%**
DM	CM	AE	EG
SC	EX	DS	IE
CO	SU	MH	LB
SE		DV	PE
		CE	QS
SUPPXX			SC
RELREC			VS
FA			

(Start and Stop Dates)

Trial Design	**What do the patients go through?**	TA, TE, TV, TI, TS

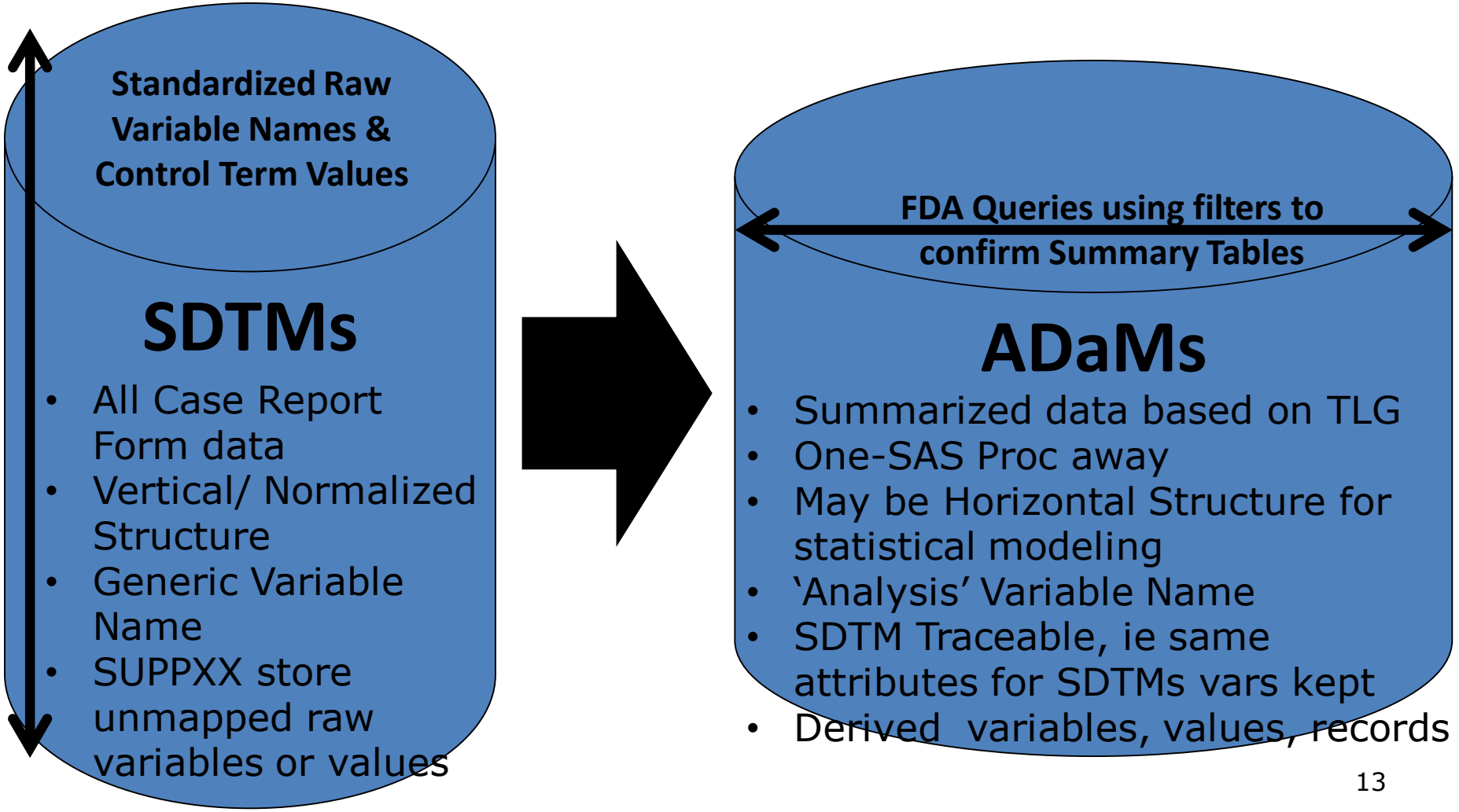
Seven SDTM Classes – Help to Map data

Question	Class	Domain	SUPP XX	Control Terminology
What is the study design?	1) Setup	TA	N/A	PLACEBO, SCRNFAIL
Who is enrolled and when are they evaluated?	2) Demographics and Visits	DM, SV	SUPPDM	F, M, U
What prescriptions did they take?	3) Interventions	EX, EC, CM	SUPPEX	TABLET
What and when did AEs happen?	4) Events	AE, DS, MH	SUPPAE	MILD, MODERATE, SEVERE
What measurements were collected?	5) Findings	LB, EG, SC, VS, DA	SUPPLB	Y, N, U
What relationships exist between domains?	6) Relationships 7) Findings About	RELREC	N/A	N/A

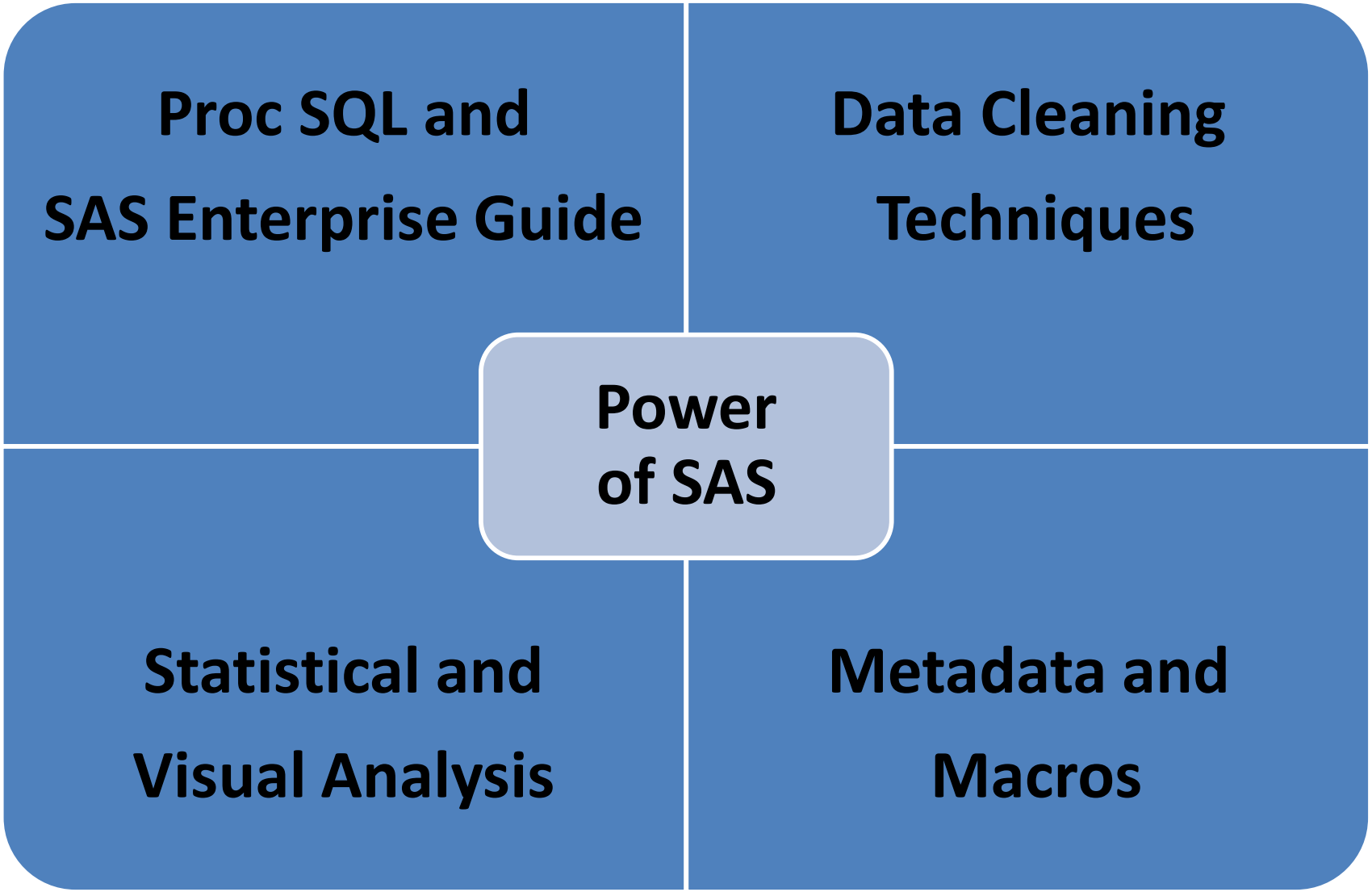
Compare and Contrast SDTM and ADaM structures

Best Practices

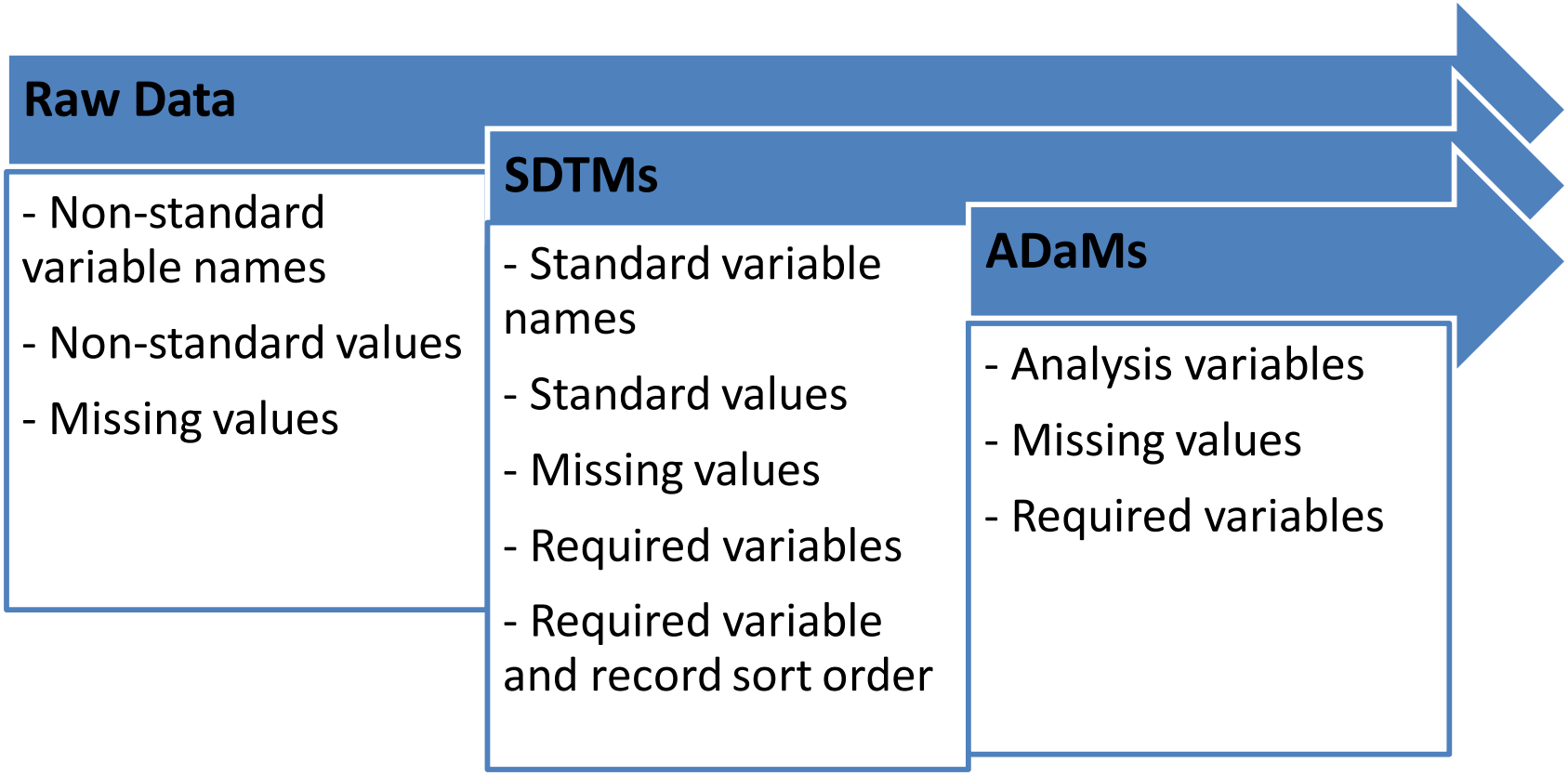
1. Create SDTMs from all case report form pages
2. Design ADaMs with required variables to create tables from shells
3. Determine mapping from SDTMs to required ADaMs



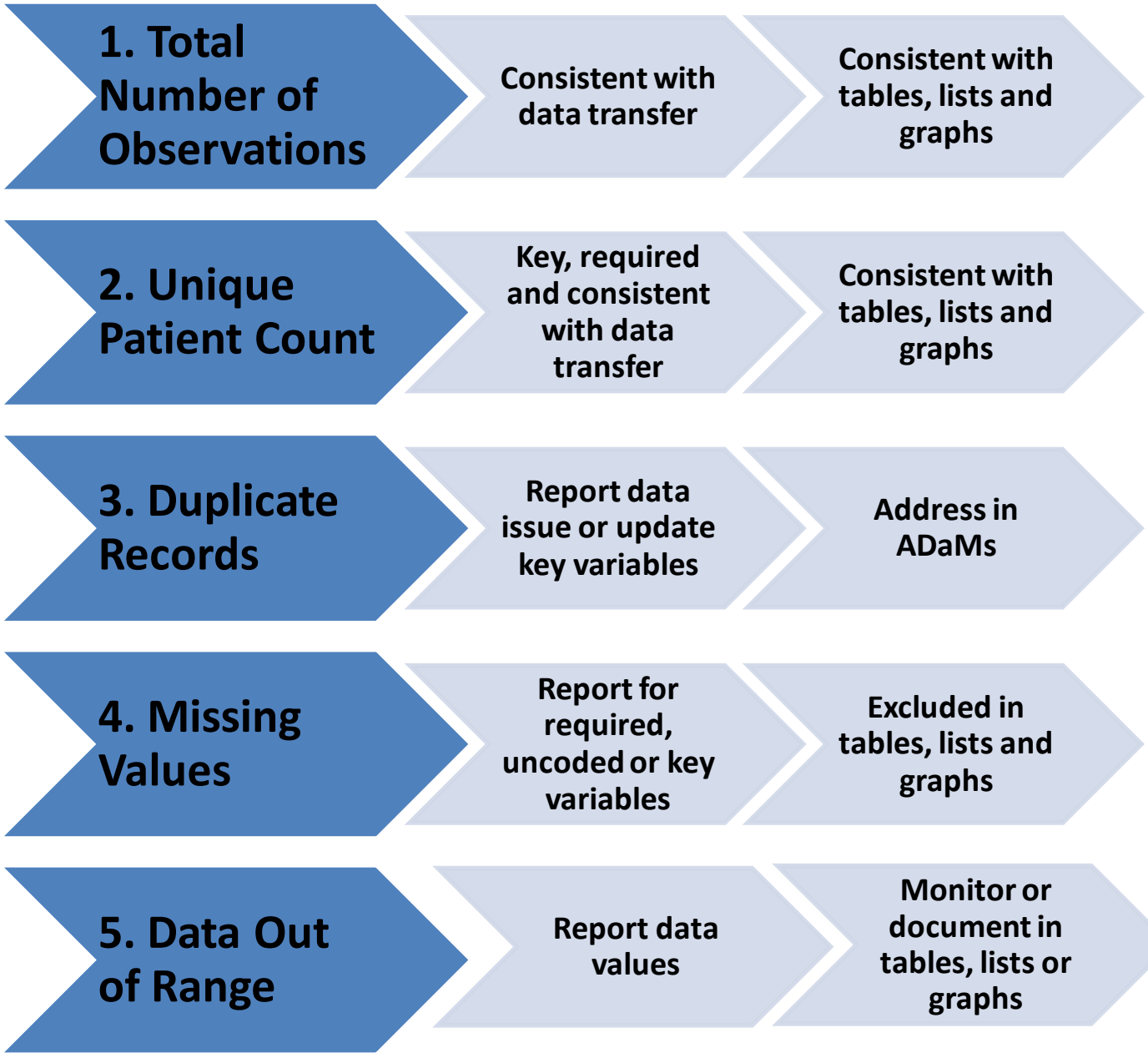
Better SAS Programming Techniques



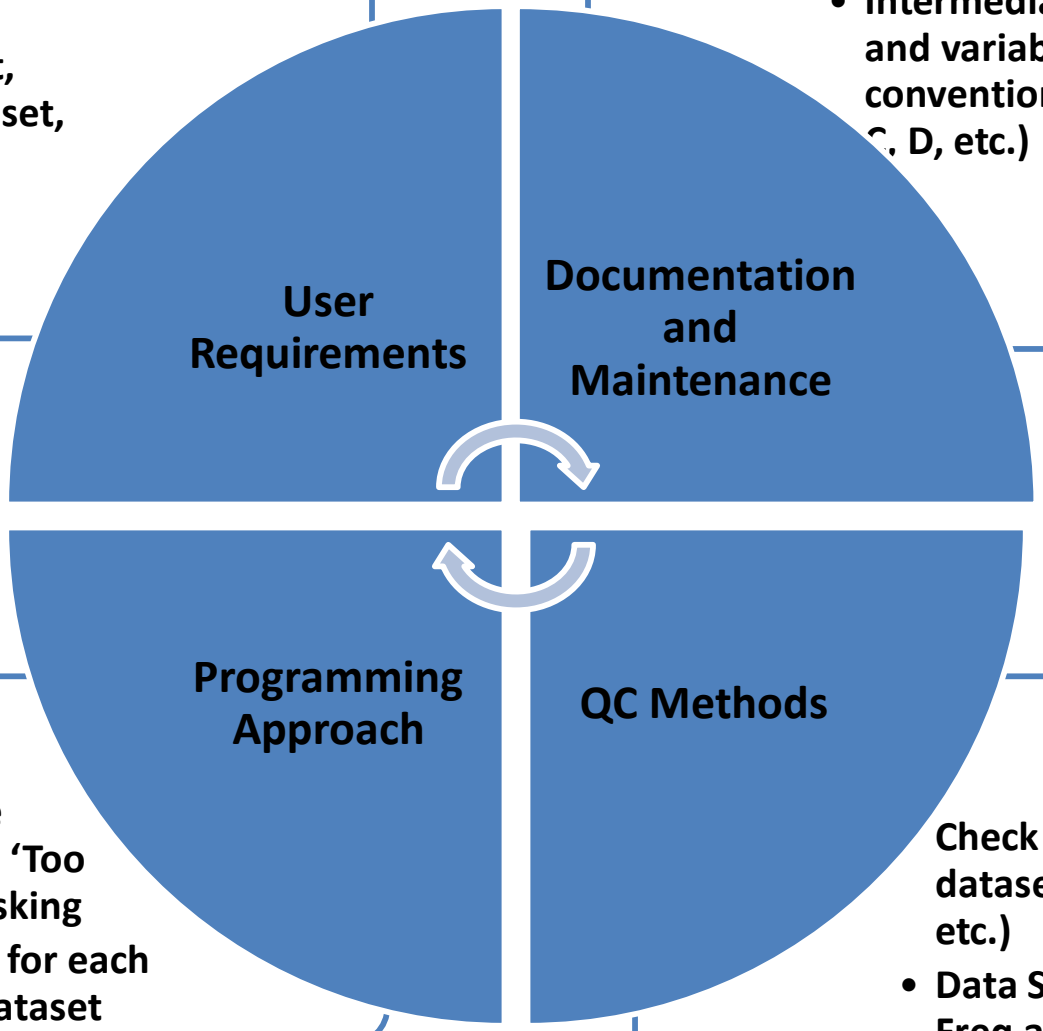
Raw to SDTMs to ADaMs: Extracting Dataset Vitals
Prevents loss of data and addresses data issues



Know Your Data: Unit Level Dataset Vital Stats



Effective Unit Testing Concepts for Proc SQL



- Purpose
- Assumptions
- Tasks (Dataset, Variables, Subset, etc.)

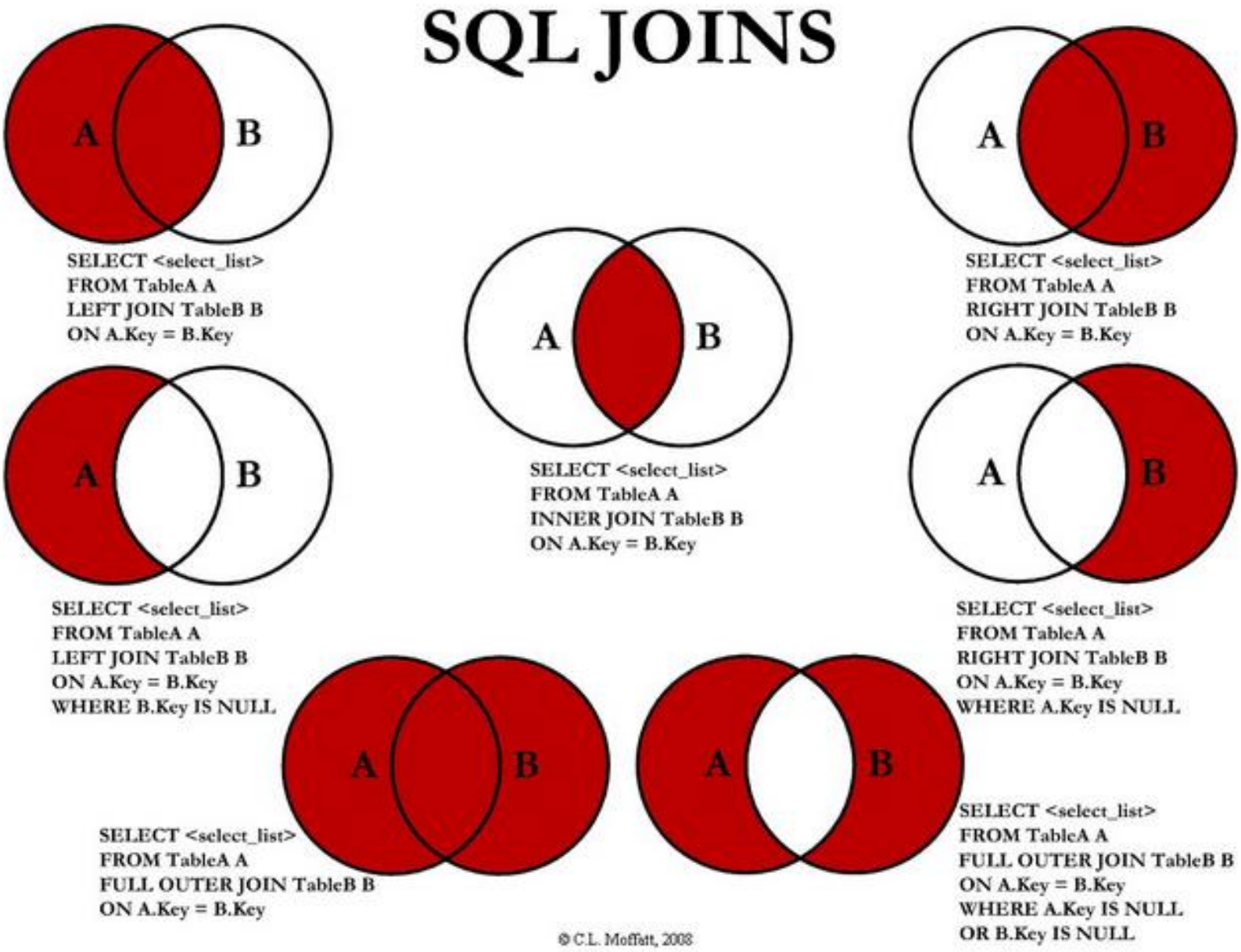
- Program Header
- Intermediate dataset and variable naming convention (A1, A2, B, C, D, etc.)

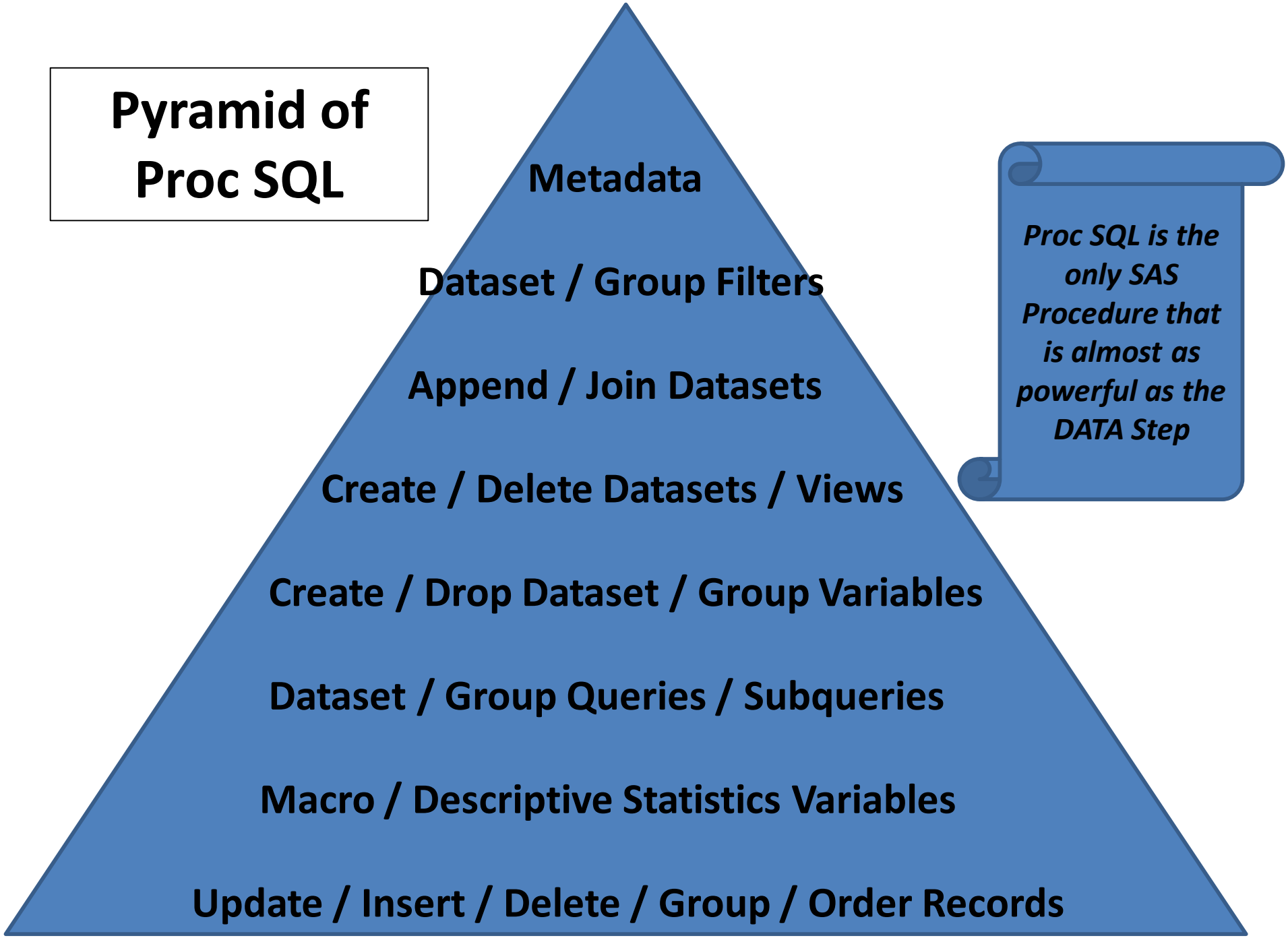
- Control is more important than 'Too much' multi-tasking
- Add comments for each intermediate dataset

Check each intermediate dataset (vars, obs count, etc.)

- Data Step, Proc Print, Proc Freq and Proc Means

Master Proc SQL to Join Datasets




Pyramid of Proc SQL
Metadata
Dataset / Group Filters
Append / Join Datasets
Create / Delete Datasets / Views
Create / Drop Dataset / Group Variables
Dataset / Group Queries / Subqueries
Macro / Descriptive Statistics Variables
Update / Insert / Delete / Group / Order Records
Proc SQL is the only SAS Procedure that is almost as powerful as the DATA Step

Something for nothing? Adding group descriptive statistics

SAS Blog

Sunil Gupta | JUNE 20, 2012

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Can you actually get something for nothing? With PROC SQL's subquery and remerging features, yes, you can.

	Name	Sex	Age	Height	Weight	sexn
1	Judy	F	14	64.3	90	
2	Jane	F	12	59.8	84.5	
3	Joyce	F	11	51.3	50.5	
4	Barbara	F	13	65.3	98	
5	Carol	F	14	62.8	102.5	
6	Mary	F	15	66.5	112	
7	Louise	F	12	56.3	77	
8	Alice	F	13	56.5	84	
9	Janet	F	15	62.5	112.5	
10	Philip	M	16	72	150	
11	James	M	12	57.3	83	
12	Henry	M	14	63.5	102.5	
13	John	M	12	59	99.5	
14	William	M	15	66.5	112	
15	Alfred	M	14	69	112.5	
16	Jeffrey	M	13	62.5	84	
17	Thomas	M	11	57.5	85	
18	Ronald	M	15	67	133	
19	Robert	M	12	64.8	128	

Count of females

Count of males

Proc SQL Subquery Linked by Group Variable

```
proc sql;   create table class2 as
  select  a.*,
  b.sexn
  from sashelp.class as a
  left join
  (select
   sex,
   count(sex) as sexn
   from sashelp.class  where sex > ' '
   group by sex
   ) as b on
  a.sex=b.sex;
quit;
```

1. Select all master variables
2. Include the new group descriptive statistics variable
3. Apply LEFT JOIN to keep all master records
4. Create internal dataset using subquery
5. Select or create grouping variable
6. Apply one or more summary functions
7. Link internal dataset by grouping variable

Apply Anatomy of Summary Reports

(WHAT: Details or Summary)

Listing / Table

(WHO: Focus Group)
(WHEN: Time Frame)

Filter / Order / Sort / Group

(Drug A is better than B)
(Drug A and/or B causes C outcome)

Objective

(Product A sales are improving)
(Product A is more popular than B)

Rows / Columns / Overall Variables

(HOW: Compare Groups, Time Periods)

Details / Counts / Statistics

(WHY: Confirm, Conclusion)

SAS Procedures to address Statistical Questions

Table 2. Classification of Statistical Tests (or P-Values) for Clinical Trials with Two Independent Treatment Groups

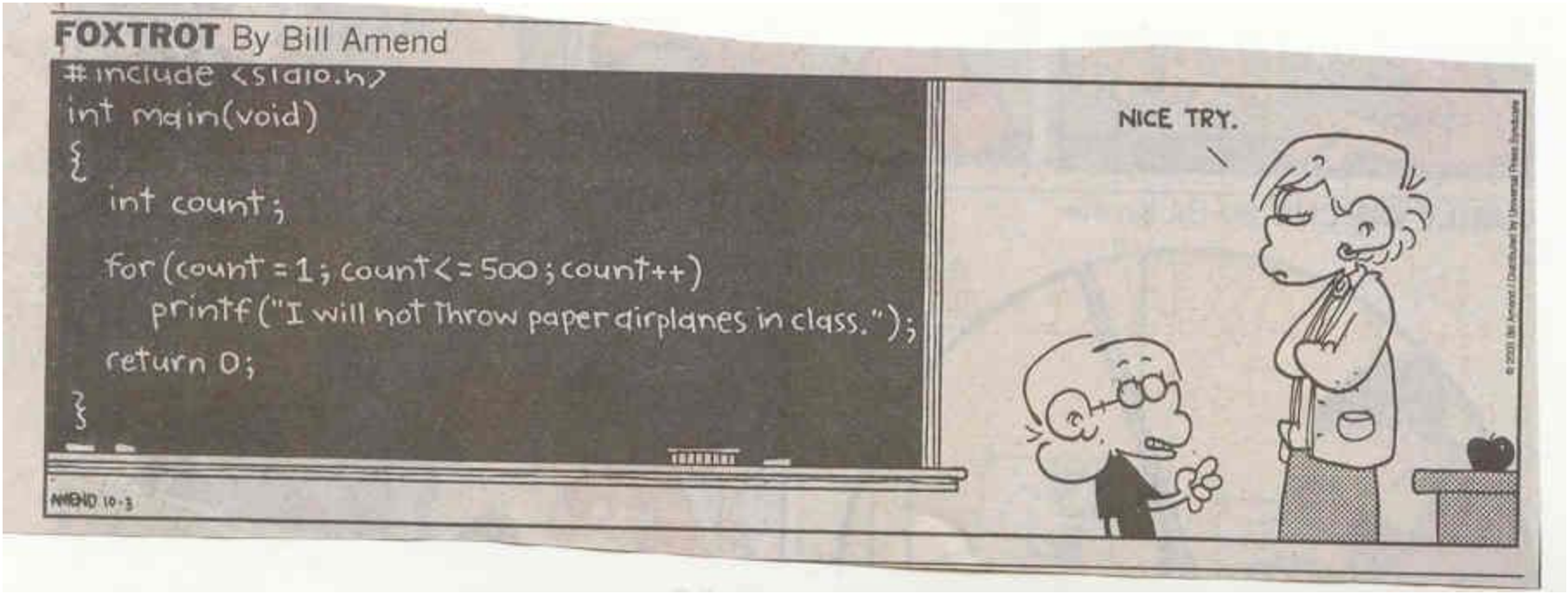
Type of Key Variable	Other Variables Included	Statistical Tests (SAS Procedures)	
		Parametric	Nonparametric
Category	Treatment	Chi-square (Pearson or continuity adj.) (PROC FREQ)	Fisher's exact test (PROC FREQ)
	Treatment + Others	CMH with table score (PROC FREQ) Logistic Regression (PROC LOGISTIC or PROC CATMOD)	CMH with rank score (PROC FREQ)
Quantitative	Treatment	Unpaired t test (PROC TTEST)	Wilcoxon rank-sum test (PROC NPAR1WAY)
	Treatment + Others	GLM (PROC GLM)	GLM with rank-transformed data (PROC RANK + PROC GLM)
Survival	Treatment or Treatment + Others	Chi-square (PROC LIFEREG)	Log-rank test (PROC LIFETEST)
		Cox proportional hazards model (Semiparametric) (PROC PHREG)	

One-Proc Away ADaM gives power to query by subsetting, grouping and analyzing to answer questions

Metadata Saves Time – What are *you* waiting for?

Using metadata will result in saving time to apply standards, automation and checks

Create Macros to Automate and Standardize the Process so that you can focus on more Challenging and Complex Tasks



How Cloud-Based Tools Can Help With FDA Compliance

Source: Life Science Leader

By Sunil Gupta, founder, www.SASSavvy.com and senior SAS/CDISC consultant, Gupta Programming.

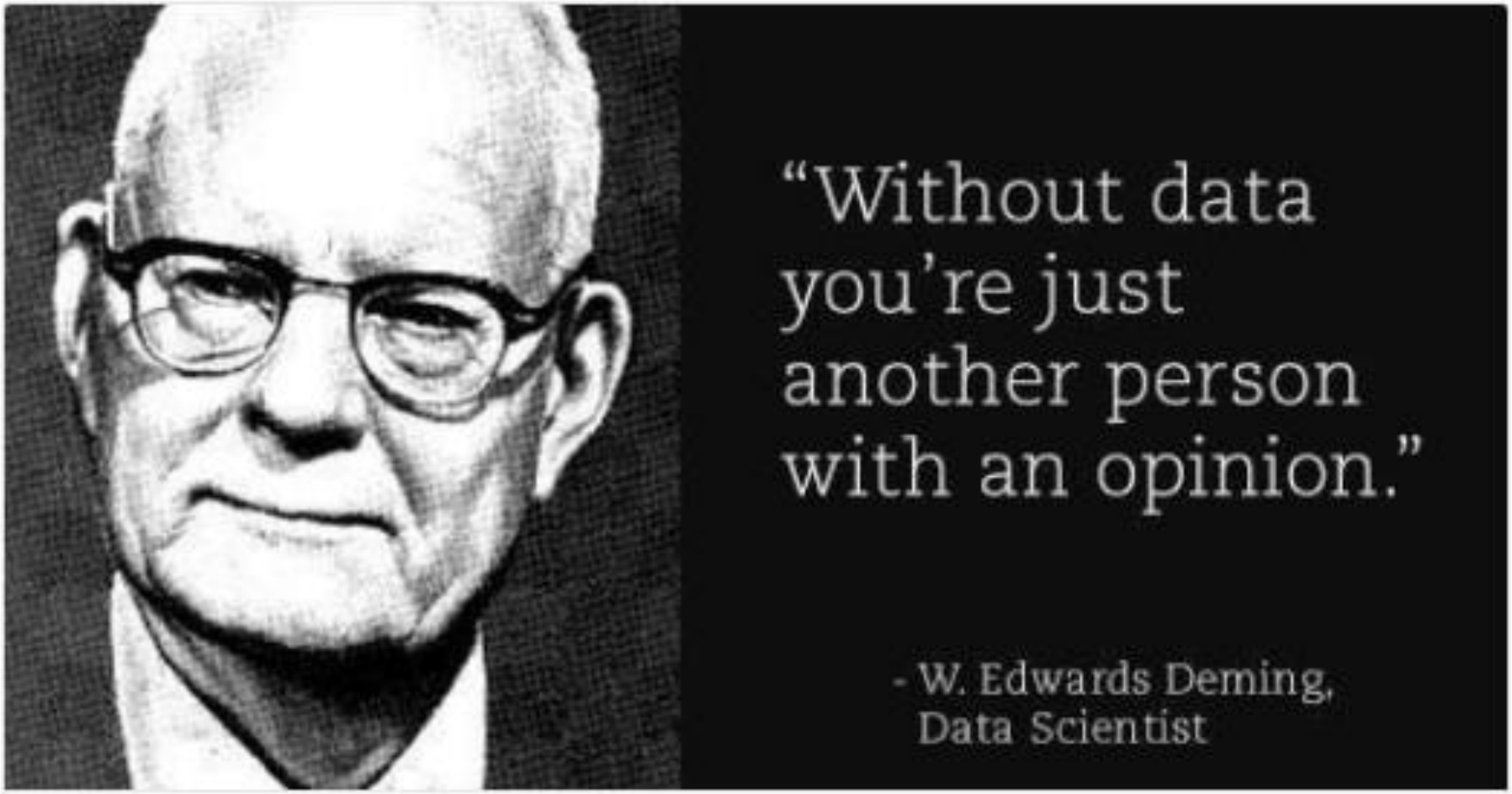
These days, enforcing FDA compliance and mentoring new team members are more challenging than ever, thanks to a workforce that is more remote, international, and diverse. Additionally, today's Internet technology is more global, sophisticated, and secure. With these changes, pharmaceutical companies need to adapt to grow and ride the cost-conscious trend just to survive. Cloud-based tools, such as wikis, offer a paradigm shift in project management, FDA compliance requirements, and job aids for mentoring new employees.

Practice Makes Perfect

Sunil Gupta and Mandyam Srirama at Quintiles offer some guidelines on making the most of training for statistical programmers

Sunil K Gupta is the Associate Director of Statistical Programming at Quintiles in Thousand Oaks, CA. He has been using SAS® software for over 14 years and is a SAS Base Certified Professional. He was the programme chair for the Western Users of SAS Software conference in 1998 and a speaker at numerous SAS User Group International and regional conferences as well as corporations. Sunil has over 50 publications to his name, and. in addition, he teaches the SAS course Best Practices in SAS Statistical Programming for Regulatory Submission.

Be in the Know - ‘Clinical’ Data Scientist



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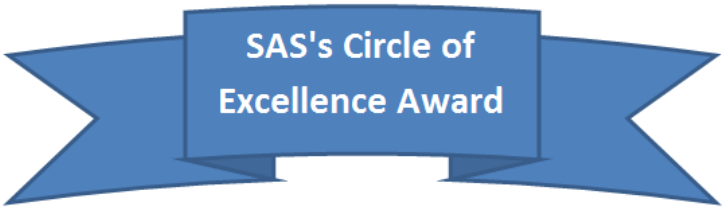
Email me for links to my SAS Tips and Articles



Cytel

Best to apply Defensive Programming Techniques

Minimizing risk of bad data: a cross-industry problem

2

By Waynette Tubbs on SAS Users | March 6, 2012 SAS Events

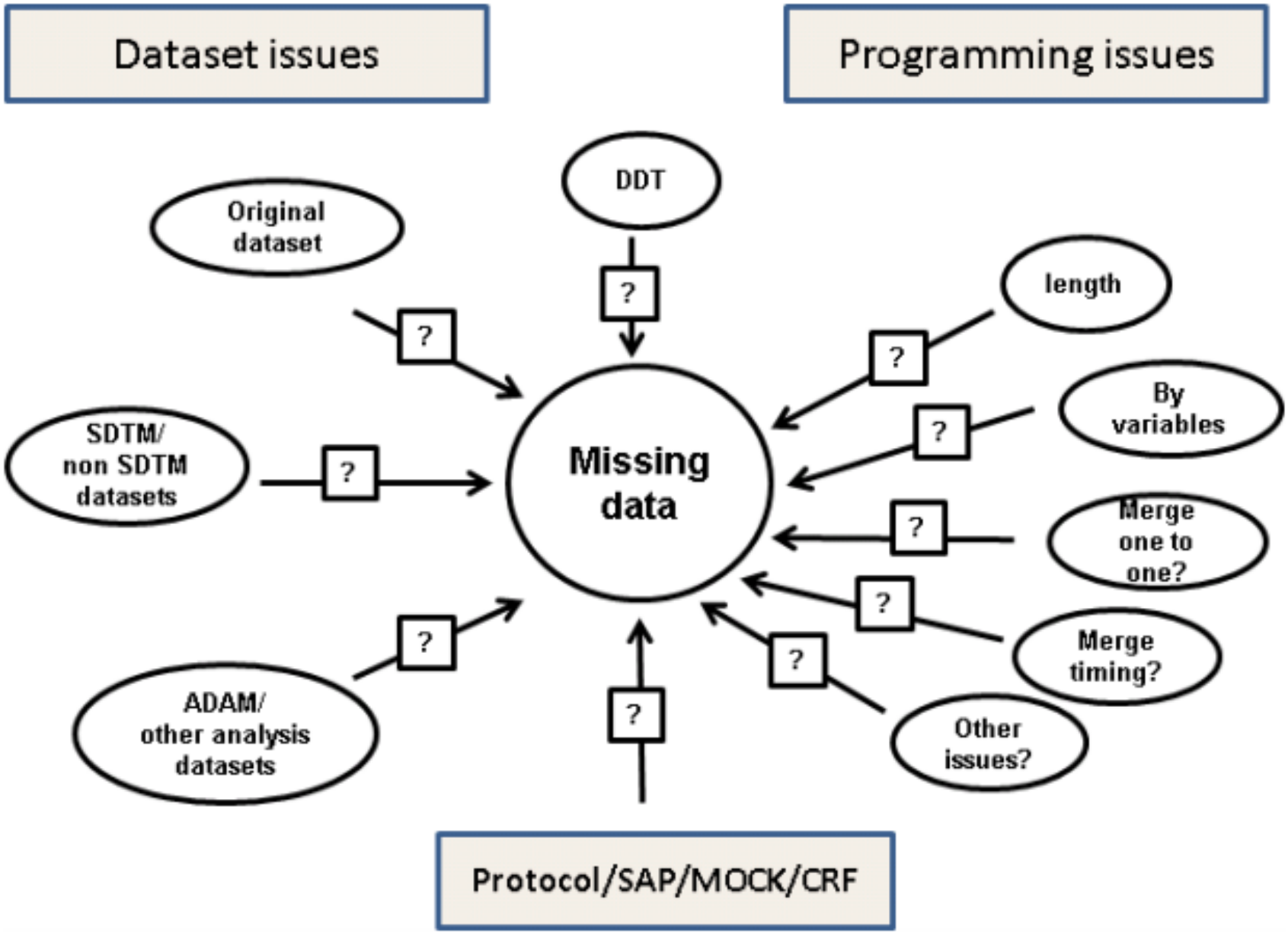
Sunil Gupta

"Bad data does exist," says Sunil Gupta, SAS author and Global Corporate Trainer, Gupta Programming. Gupta is an expert in the pharmaceutical and medical device industry, but he volunteered this week to speak to an audience of SAS users in the insurance and financial services industries about minimizing the impact and risk of bad data. He believes that many of the processes, code and ideas used in the pharmaceutical industry can be applied across other industries with equal success.

Gupta began by showing examples of bad data encountered in the pharmaceutical industry (interestingly, these are also types encountered in other industries):

- duplicate records
- missing values
- start dates are after stop dates
- invalid values for variables

Challenges: Sources of Missing Data: Dataset and Programming Issues



Pay Attention to Details

SAS Tip: Do You Understand Differences between Where vs. If

Usage Note *24286:* When do I use a WHERE statement instead of an IF statement to subset a data set?

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