

Chrestos – Die grüne CRO

Twice As Much Ain't Twice As Good: Is Double Programming Really The Gold Standard We Think It Is?

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The Grass is Always Greener on the Other Side



Would you trust an aeroplane whose software was developed using **double programming (DP)**?

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The Evolution to the Gold Standard

Prior to 1990s:

- Single programming, **manual** review checks
- **Inefficient** standard practice, prone to oversight and error



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- Inefficient** standard practice, prone to oversight and error

During 1990s:

- Complexity** of clinical trials **increased** → higher standards of data quality & higher regulatory scrutiny
- No clear turning point: **introduction of DP**, widespread adoption



What's the regulatory take on DP?

The Evolution to the Gold Standard

FDA:

- Strong focus on documentation, **reproducibility** & **reliability** of software
- **Appropriate validation** of programs

“Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses.”

*“The main purpose of requesting the submission of these programs is to **understand the process** by which the variables for the respective analyses were created and to **confirm the analysis algorithms and results.**”*

The Evolution to the Gold Standard

EMA:

*“The sponsor should ensure that **appropriate** and **documented quality control** of statistical programming and data analysis is implemented.”*

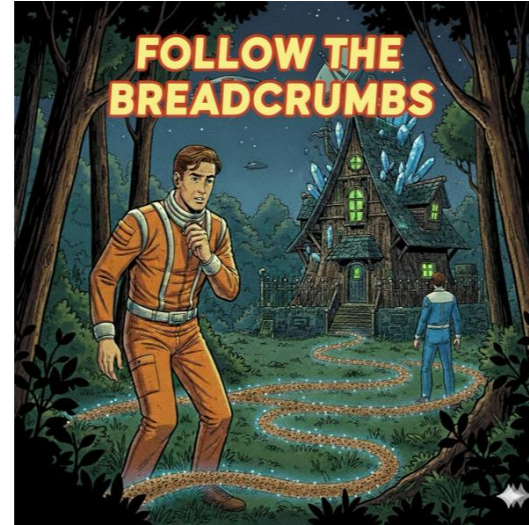
*“The sponsor should ensure the **traceability** of **data transformations** and **derivations** during data processing and analysis.”*

- Similar information from PMDA and relevant guidelines (ICH E6/E9)
- **If DP was not explicitly required by regulators, why did „they“ come up with it?**
- DP easy to implement technically, to document, to trace & to understand

Because they **could**

Pitfalls & Prerequisites

- Be careful when re-using programs → it's **independent DP**
- If more complex, involve experienced programmers



- Specs need to be precise to avoid misinterpretation
- Documentation is important → **traceability**

Alternatives & Future Trends

Re-think validation beyond conventional DP:

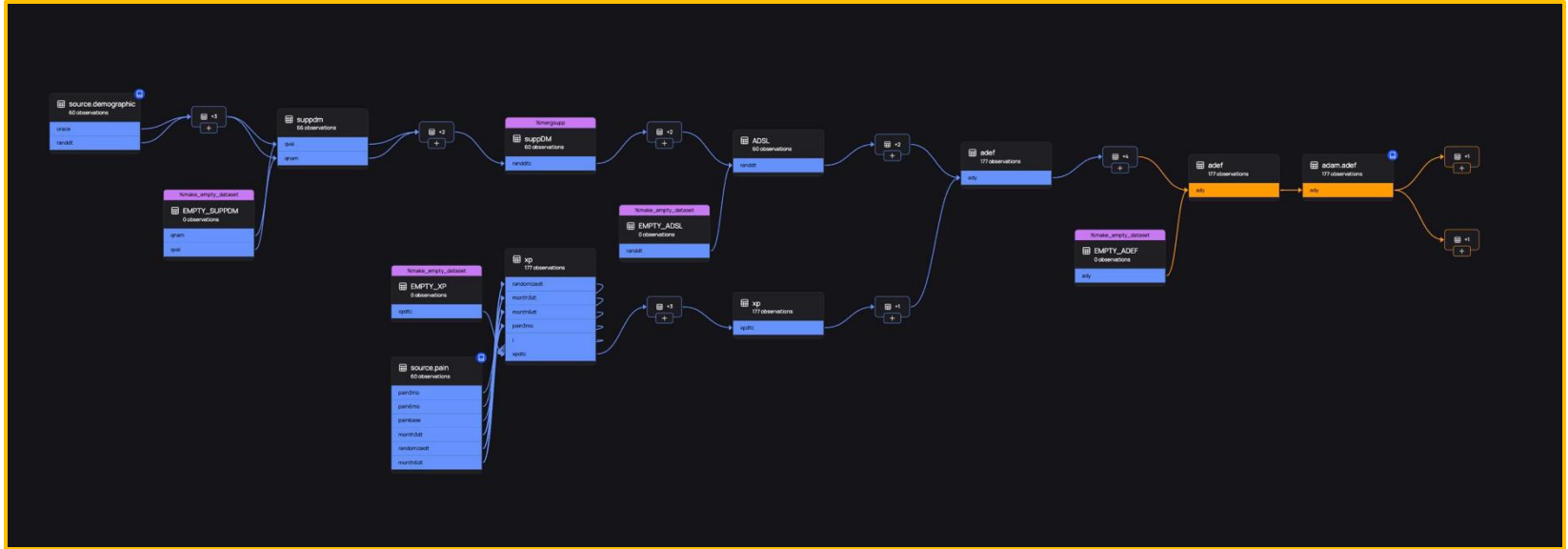
- Start with **code** as the **source of truth**
- **Code traceability** captures every variable, dataset, format, codelist, result and transformation in a study
- **Reproducibility** made easy
- **Transparency, trust and confidence** in submissions

Our tool of choice:



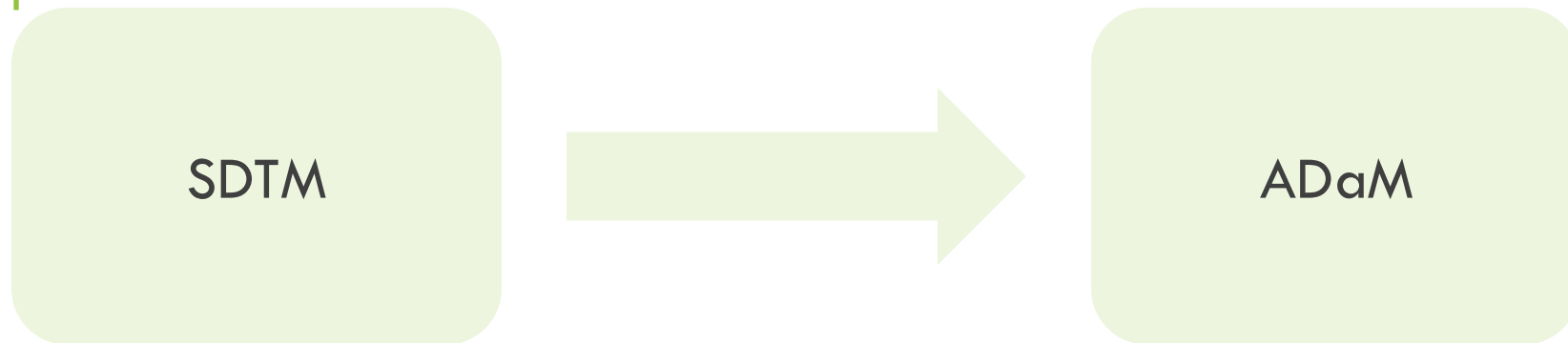
Alternatives & Future Trends

Use case 1: Knowledge Graphs



Alternatives & Future Trends

Use case 2: **Automation**



Rule: for all rows in ADaM records must be equal to SDTM source

Mapped: 50%

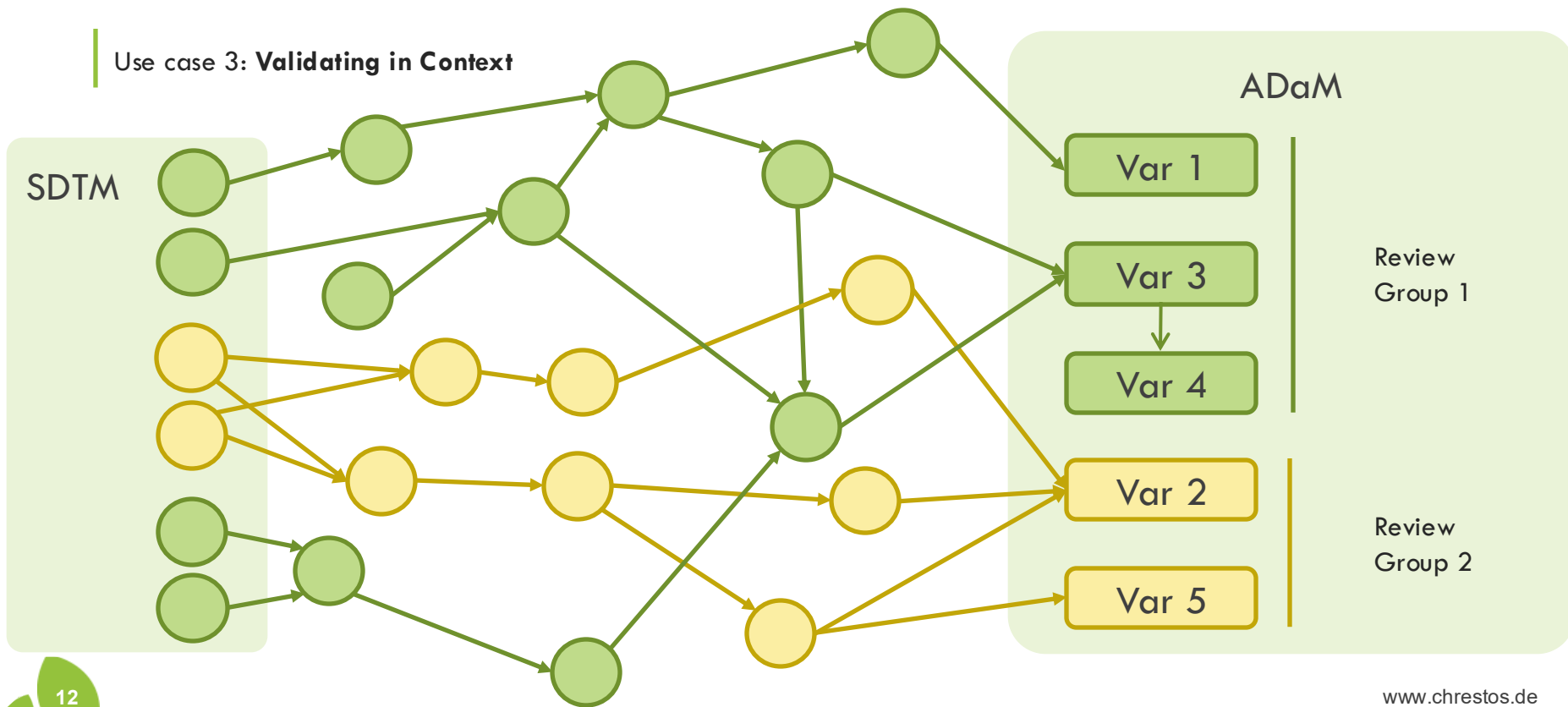
Standard Macro: 30%

Custom: 20%

Rule: standard macro must be correct & must not be re-defined

Alternatives & Future Trends

Use case 3: **Validating in Context**



Alternatives & Future Trends



Use case 3: Validating in Context

Level ▾	Domain ▾	Variable	Conditions	Status ▾
▼ SDTM				
	> 🗃️	ae		
	▼ 🗃️	dm		
▼ Review Group “Trial Arm”				🕒 Review
	🗃️	actarm	Description of Actual ...	
	🗃️	actarmcd	Actual Arm Code	
	🗃️	arm	Description of Planned...	
	🗃️	armcd	Planned Arm Code	
▼ Review Group “Age”				🕒 Review
	🗃️	age	Age	
	🗃️	ageu	Age Units	

Alternatives & Future Trends

A peek into the crystal ball

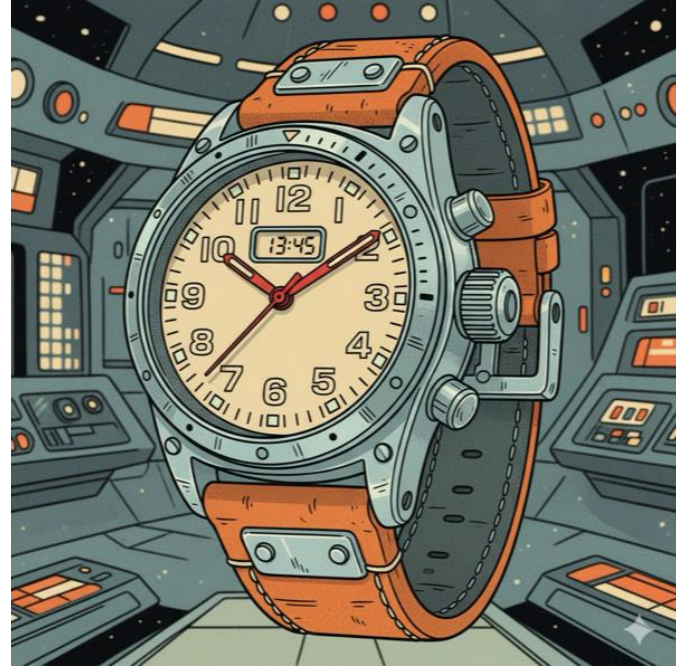
- Less code writing / more **understanding** data, domains & **concepts**
- Develop / improve **communication skills**
- **Language agnostic** programming via **agentic AI**



Alternatives & Future Trends

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Double Programming is not dead, but...



Takeaways:

- Re-thinking **status quo** of QC using tech we already have
- No need to erase DP, but amount to decrease
- Combination of **code traceability** + **agentic AI**

The role of statistical programming:

Bridge the gap from raw data to SDTM, ADaM and outputs in the highest quality possible – keep that in mind and adapt based on the circumstances



Thanks for your
attention!

