

Specifications nuisance or core?

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Agenda

- Context
- Commonly stated challenges
- Some terminology
- A look at the environment we work in with a focus on customers and our deliverables
- Quality requirements, regulations and applied methodology
- The way we organize ourselves
- Some reflections and proposals for discussion

Context

- This presentation focuses on statistical programming activities as they apply to the process of analysis and reporting clinical trial data within clinical teams.
- This discussion is around programming specification as they appear in the context of a Statistical Analysis Plan (SAP) and the reporting of clinical trial data.
- The thoughts put forward in this presentation have the **purpose to stimulate a discussion** within the professional community of “Programmers in the Pharmaceutical Industry” about future perspective in the clinical development area
- This presentation reflects my **personal thoughts and observations** from discussions held with various stakeholders and may not reflect the views held by past or current companies.
- More questions than answers ...

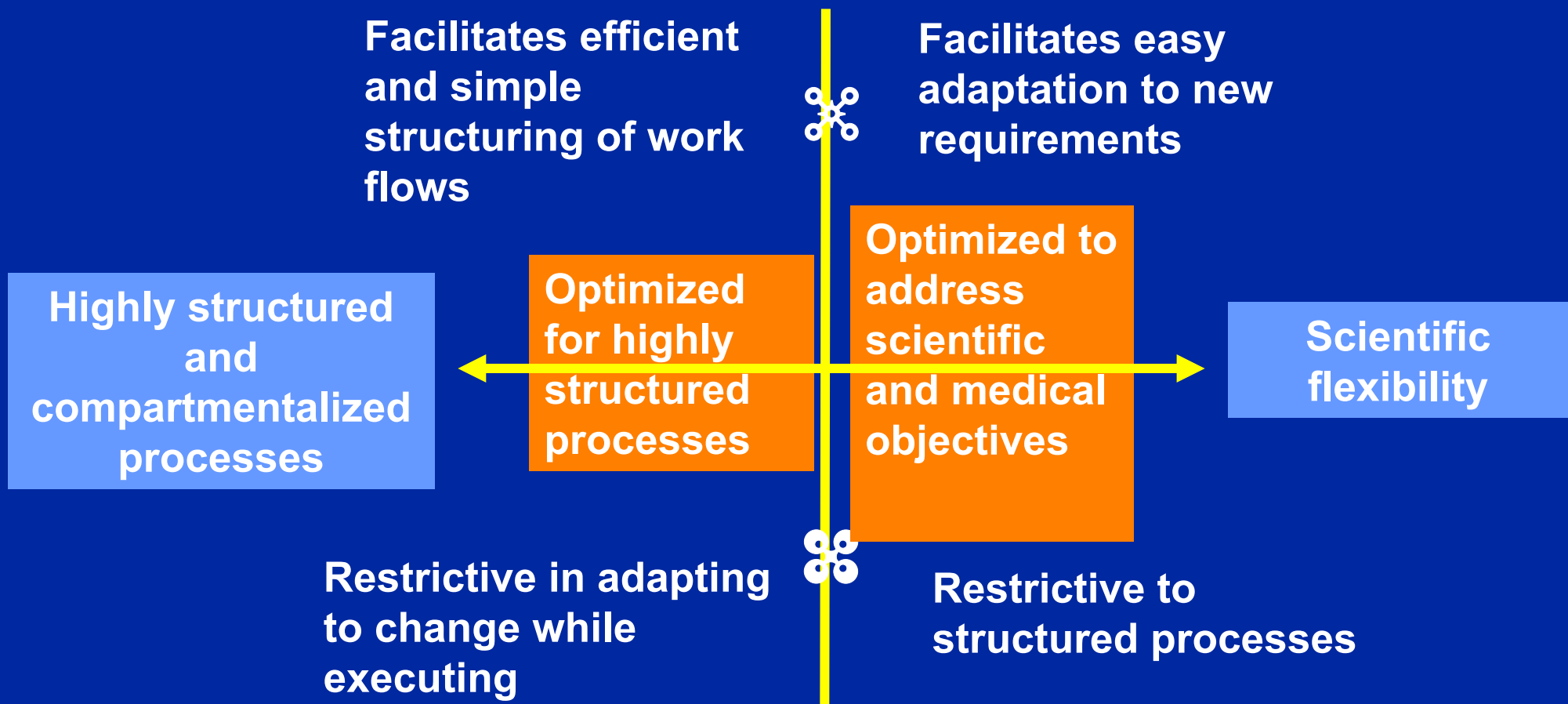
Commonly stated Challenges

- User requirements are **not available early enough** and sufficient details even less
- User requirements constantly change and are increasing in volume
- Required data assumptions are not fully known until all data is available (shortly before data base lock)
- **Extensive documents** (generally Word documents) have to be written, taking a lot of time which is lacking in the execution, and no one is really reviewing these document in sufficient detail to ensure that they are actually correct.
- **Alignment of change control/versioning** of requirements/specifications and implementation are challenging and time consuming

Terminology on specifications in this presentation

- Various can be the type and focus of specifications:
 - User requirements specification, functional specifications, design specifications, technical specifications, programming specifications
- For simplicity this presentation is focusing mainly on two aspects:
 - **User requirements specifications**: documentation based on a strong customer input, e.g. mock tables shells, general data handling conventions, derivations dependent on clinical input
 - **Programming specifications**: documentation with a focus on implementation by the programmers, e.g. analysis dataset specifications, additional information completing mock shells

A Fundamental Paradox of Clinical Development



The customer

- Who is the customer **Statistics or is it Clinical Science?**
 - Both
 - Ultimately Clinical Science is the customer and play an important role in influencing the user requirements as well as changes and extensions to them.
- How close are we to Clinical Science?
 - Are we as close such that the goal of reporting clinical study data (text and data displays) is seen as **a joint effort?**
 - How often are we sitting down **together to discuss** about requirements and look at proposals?
- How well is the **understanding** of each others requirement and work processes?

The products that are to be delivered

- Provide data analysis in form of **reports to answer questions** posed within a clinical trial with the data collected.
- **User requirements** from a Clinical Science perspective
 - Timely delivery of defined analysis reports meeting quality standards
- **Consequences** for quality requirements from the user point of view
 - The data is represented in an adequate and logically correct manner
 - The analysis is transparent and can be reproduced
- **Prerequisites** to be able to generate and provide those deliverable
 - Analysis reports are sufficiently defined
 - Clarity of handling data assumptions for missing data and potential data permutations
 - **The above are available in time**

Specifics in the clinical trial reporting process

- The quality of the reports is based on an **interaction between data and the code** processing it
- **All possible features of the data** are not known until shortly before final execution is needed (once all data is complete for a study)
- The overall work flow process of delivering **shortly after all data is available** (data base lock) requires that everything is planned, implemented, tested and reviewed by the customer sufficiently upfront.
- Drug Development is performed in a **scientific environment** which believes in the need to adapt based on new information

The quality requirements from a deliverable perspective

- The product statistical programmers provide in most cases is not a software application
- We generate (statistical) software programming solutions to **represent data adequately and logically correct**
- Consequences for **quality requirements**:
 - Provide evidence that the outcome of a single program or combination of multiple ones accurately and effectively represent the original clinical data
 - The process of how this has been achieved and how the quality has been assured is transparent and documented
 - The process is in line with regulatory requirements (ICH E9 and FDA 21 CFR Part 11)

The regulatory point of view

- **GCP - requirement: ICH E9**
- In essence: - Decisions impacting the interpretation of the data need to be pre-defined prior to unblinding of the study to minimize interpretation bias
- The results presented need to be transparent (reproducible)
- **21 CFR part 11:**
- In essence: Traceability
 - Does not prohibit change if well controlled and as long as transparency is maintained

Along software development

- The most often referred process in statistical programming is the commonly used software engineering approach: System Development Life Cycle Model (=Life Cycle Model, Linear Sequential Model, Waterfall Model)
 - Requirements – mock shells, data handling rules, user input into derivations
 - Design – programming specifications
 - Coding
 - Test - Validation
 - User acceptance – check on deliverables
 - Final release
- There is nothing wrong with this approach ...

... with a view on our environment

- User requirements and programming specifications are needed to perform testing/validation
- But ...
- How well does the **sequential focus** fit with a more **adaptive scientific** approach?
- How realistic is it that **all user requirements** for reporting an entire study are being **defined upfront** and documented before our work can actually start?
 - Theoretically it is possible
 - Practically it appears to break down more often than otherwise
- How **inclusive** is it for interaction between customers and programmers ?

Are we using the right tools for user requirements and specifications

- User requirements and programming specifications build **extensive documentation** generally modularized (by sections or individual document) by type of specifications
 - Advantage: it is providing the general overview that is needed
 - Disadvantage: does not support a sequential approach by individual components (e.g. deliverables by domain) since approval is all or nothing
- **Change control of specifications** in alignment with programming is very difficult and extremely time consuming.
- Some parts are **typed, reviewed, retyped and changed** again (e.g. table titles and footnotes), with considerable input from customers

How should programming specifications be written

- **Functional description:** Describe in natural language referring to elements of the user requirements and the annotated CRF
 - Requires: a good understanding of the study (protocol, annotated CRF, DRAM Part I) **SURVDT = Date of death or last date patient alive**
 - **Requires** a knowledgeable programmer that is able to translate this specification into a correct program
- **Technical description:** Extension of functional specification with technical information referring to data sets, variables, conditions, and selection clauses

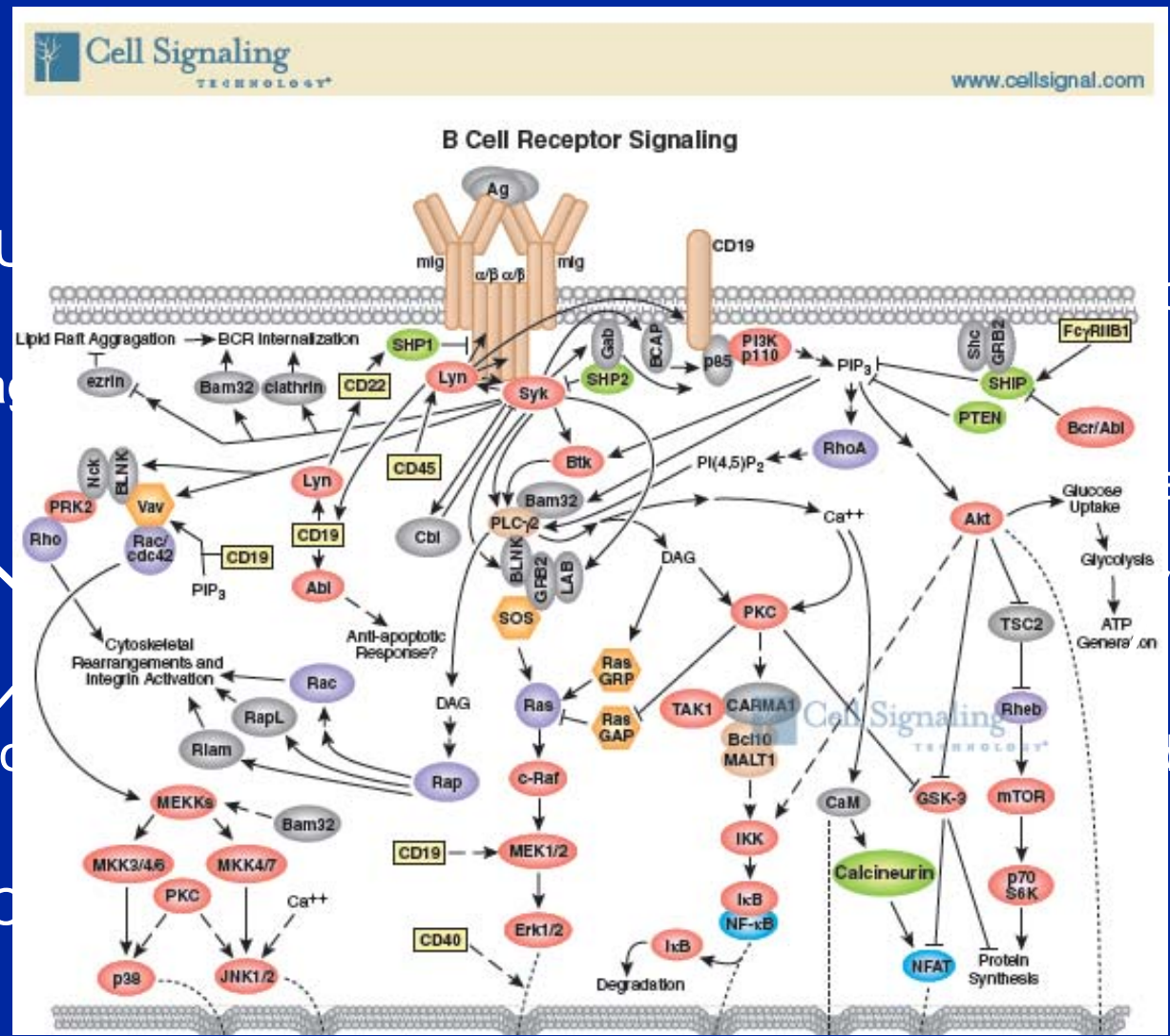
SURVDT = Date of death [datetime value at either study completion or survival follow up] or last date patient alive [last datetime value of the dates occurring on the following data panel ... <list of datasets.variables>]

- **Requires** a careful review step that the functional description matches the **technical part**

Last but not least - Specifications serve collaboration

- Reporting of clinical trial data is a **collaborative team effort**, more and more with additional challenges of virtual teams
- Specifications provide the **basis of collaboration** on what a team will have to achieve and provides a framework for work sharing
- The degree of details in the specifications are largely dependent on what is covered by **common convention** and part of the **professional profile requirements** (Knowledge of principles related to common summaries applied to reporting and handling clinical study data) and **model of work sharing**

The complexity of the dimensions



Change management

of Programmers

requirements

Standard C

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Conclusions and Proposals

- The concept of having all specified to the last detail for all deliverables before starting and implementing with no expectations to changes does not appear feasible
- Consider **stepwise more modular approach** with customer interaction on clarification for further input
 - > Requires **well designed structured programming solutions** for clinical studies/projects allowing for that
 - > Each study is different, but there is **much more in common** to focus on
 - > The entire set of specifications could be looked at as a **virtual document** with modular components which could be better linked with the modular programming design.
 - > Requires that some walls between Statistical Analysis Environment and the “customers” world where specifications are currently being written will disappear

Conclusions and Proposals

- The degree of **details required in specifications and the style** they need to be written is a function of:
 - Work sharing model
 - Quality assurance model
 - Coverage with agreed conventions (Standards) – Training on those
 - Professional profile requirements

-> There are choices to be made, or made choices have decided
- To work along with the customer interactively will always provide better products and satisfaction for all parts involved
- **Good specifications are core ... but one can make it a nuisance**