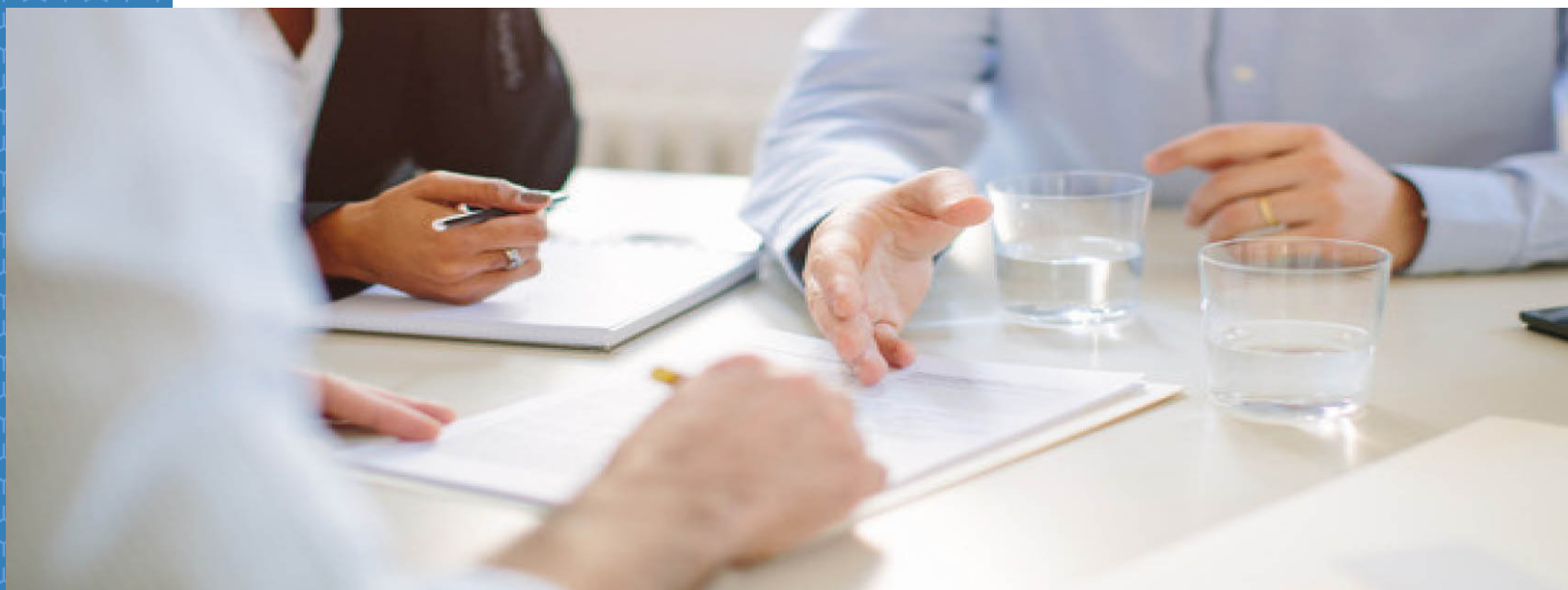




How to review a CRF - A statistical programmer perspective

**Elsa Lozachmeur, Senior Statistical programmer
PhUSE Data Handling stream, DH07
Barcelona, OCTOBER 11, 2016**

Agenda

1. Introduction

2. Risks and consequences

3. The big picture – Clinical trial document landscape

4. Real study case

5. Guidance for statistical programmers

- a. Key responsibilities
- b. Guidance for a good review
- c. Advantages of using CDISC standards

Introduction

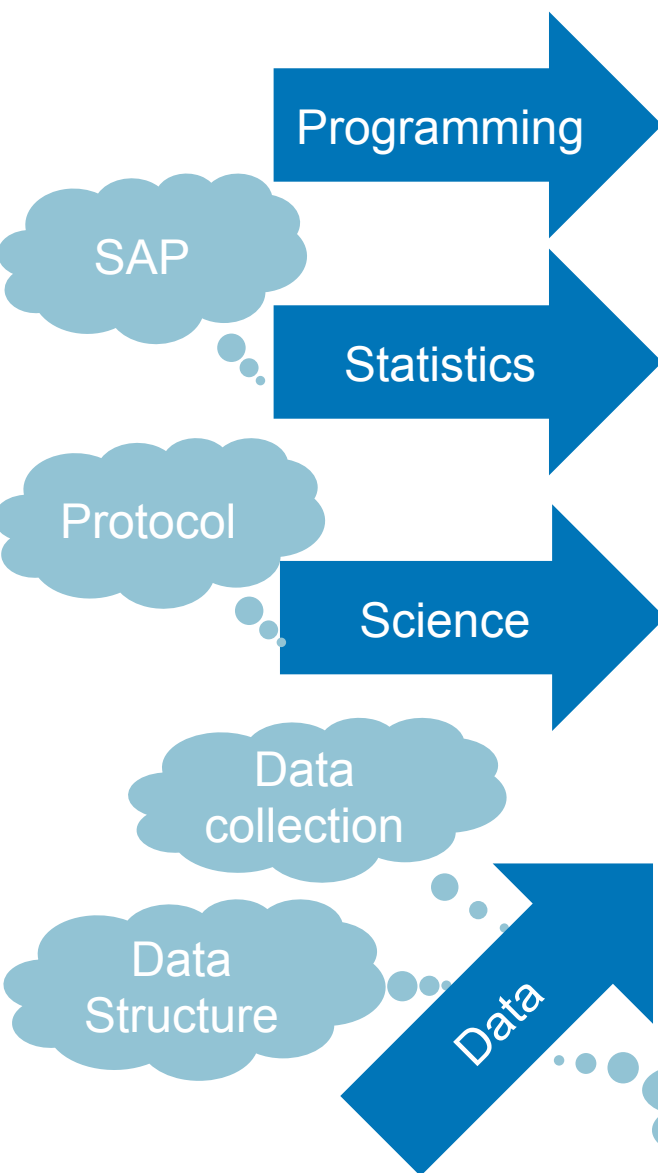


Table 14.2-1.13 Summary statistics of 6MWD (meter), by visit window

Full analysis set

Visit window	BYM338 10mg/kg (N=xxx)			BYM338 3mg/kg (N=xxx)			BYM338 1mg/kg (N=xxx)			Placebo (N=xxx)		
	Base	Post	Change	Base	Post	Change	Base	Post	Change	Base	Post	Change
Baseline												
n	Xxx			xxx			xxx			xxx		
Mean	xxx.x			xxx.x			xxx.x			xxx.x		
SD	xxx.xx			xxx.xx			xxx.xx			xxx.xx		
Minimum	xxx			xxx			xxx			xxx		
Q1	xxx.x			xxx.x			xxx.x			xxx.x		
Median	xxx.x			xxx.x			xxx.x			xxx.x		
Q3	xxx.x			xxx.x			xxx.x			xxx.x		
Maximum	xxx			xxx			xxx			xxx		
Week 8												
n	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Q1	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Q3	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Week 16												
...												

6MWD = 6 Minutes Walking Distance, SD = standard deviation.

Base = Baseline, Post = Post-baseline, Change = Post-baseline - baseline.

At each visit, only subjects with a value at both baseline and the post-baseline visit are included.

Baseline is defined as the last assessment before the first dose of study drug.

Introduction

Definition

	ID		SCREENING
	Center No.	Subject No.	Visit Name

Prior and Concomitant Medications
Please enter only one medication/trade name per line.

Any medications to report? ☐ No ☐ Yes ☐ Unknown

Name of medication

Dose per administration

Dose unit

Dosing frequency per interval

Route of administration

Reason

Start date
(DD-MON-YYYY)

End date
DD-MON-YYYY) or Ongoing at final examination ☐ Yes

-

CMG02

Epoch	Document Number	Subevent#	Page Number 12
Verified ☐ Approved ☐ Locked ☐ Frozen ☐	Page Name CONCOMITANT MEDICATIONS	Status	Version

Agenda

1. Introduction

2. Risks and consequences

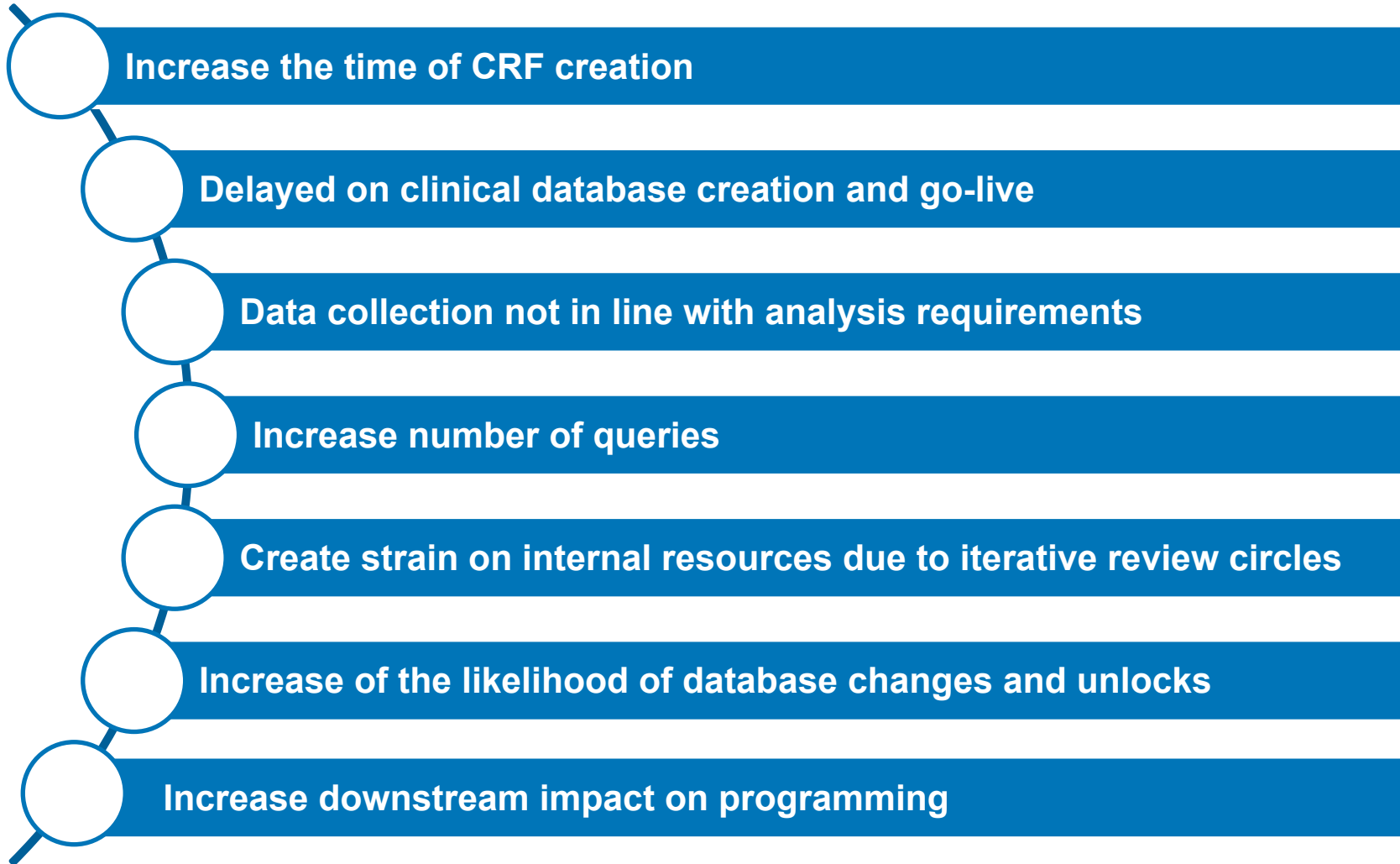
3. The big picture – Clinical trial document landscape

4. Real study case

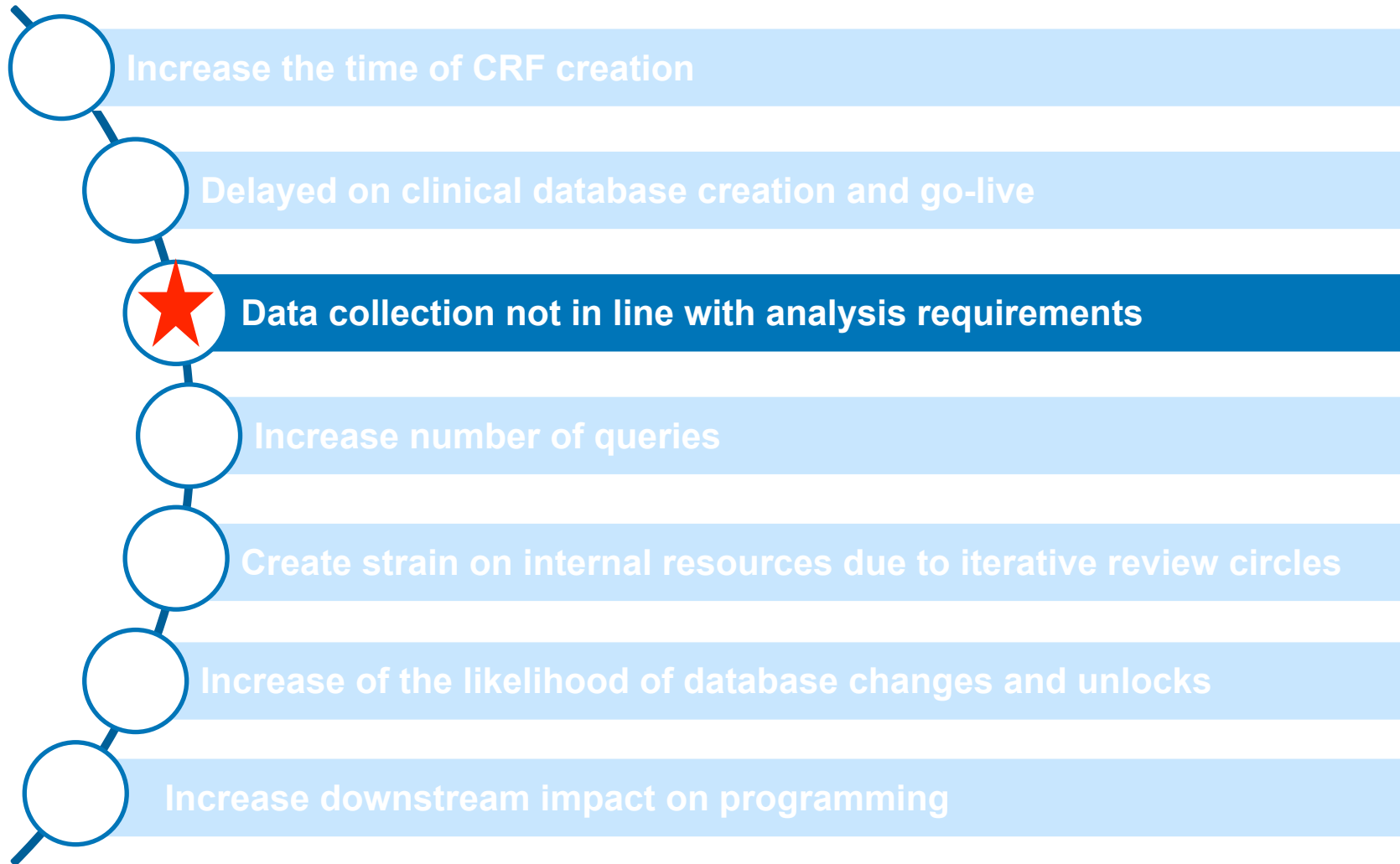
5. Guidance for statistical programmers

- a. Key responsibilities
- b. Guidance for a good review
- c. Advantages of using CDISC standards

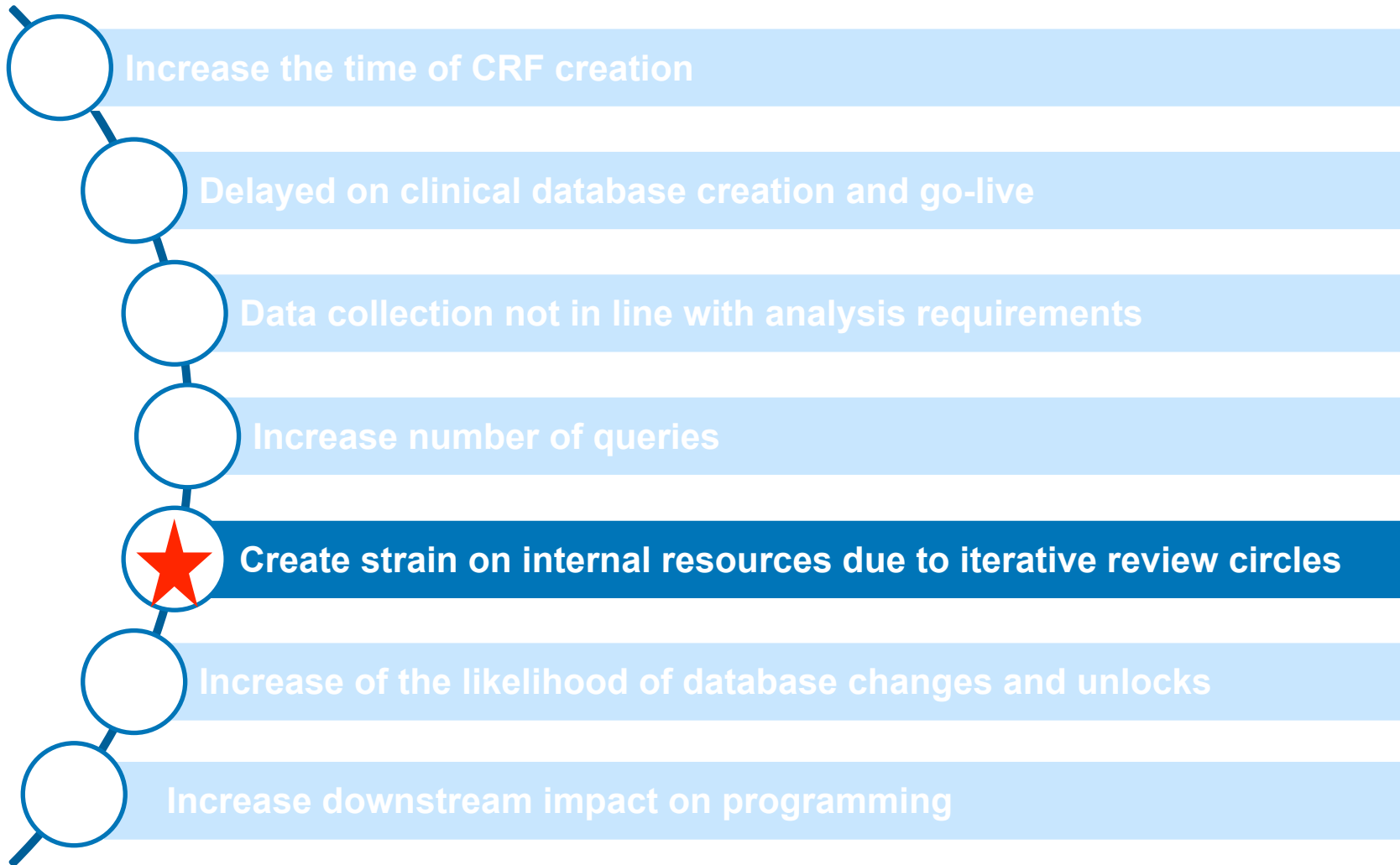
Risks and consequences



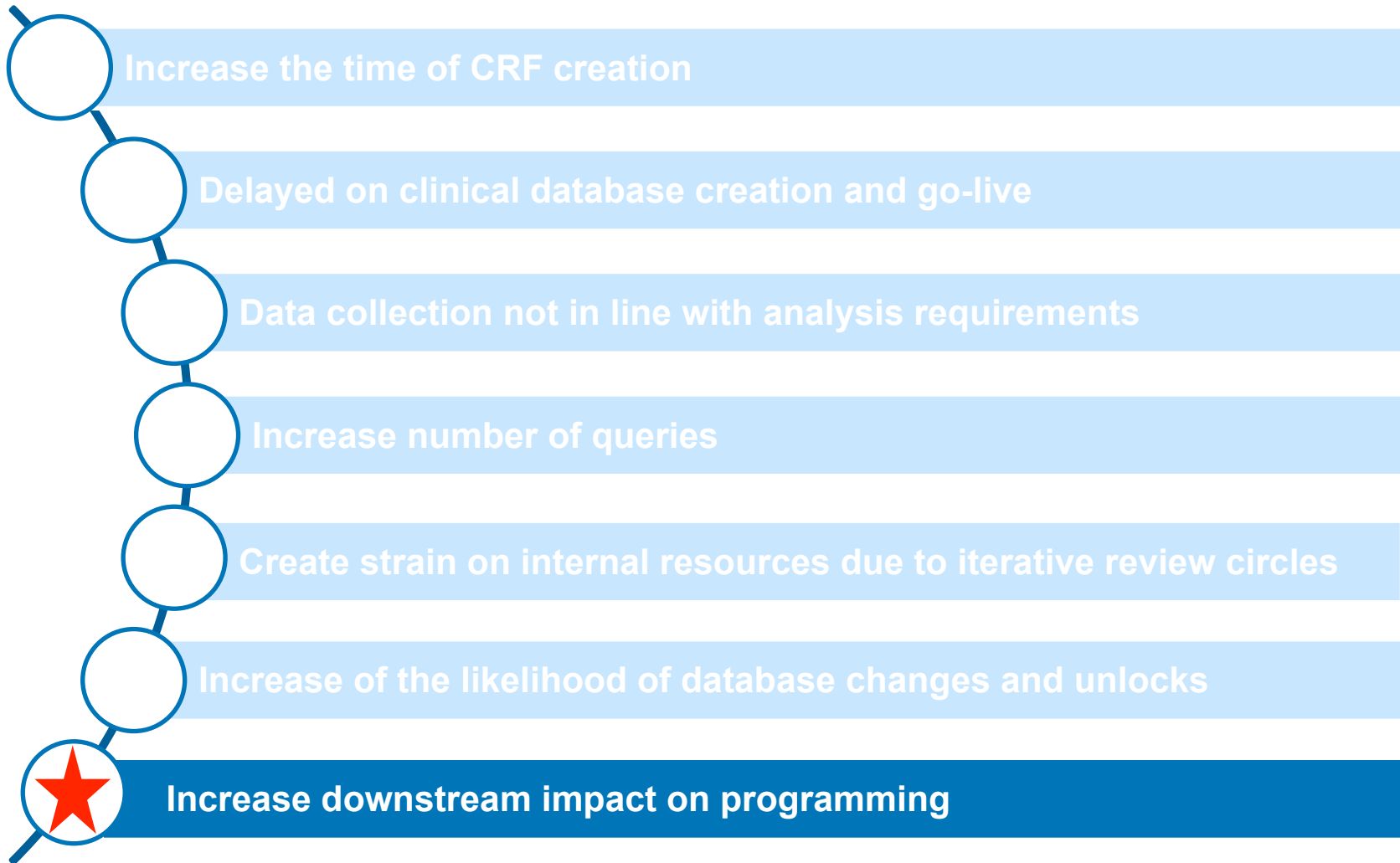
Risks and consequences



Risks and consequences



Risks and consequences



Agenda

1. Introduction

2. Risks and consequences

3. The big picture – Clinical trial document landscape

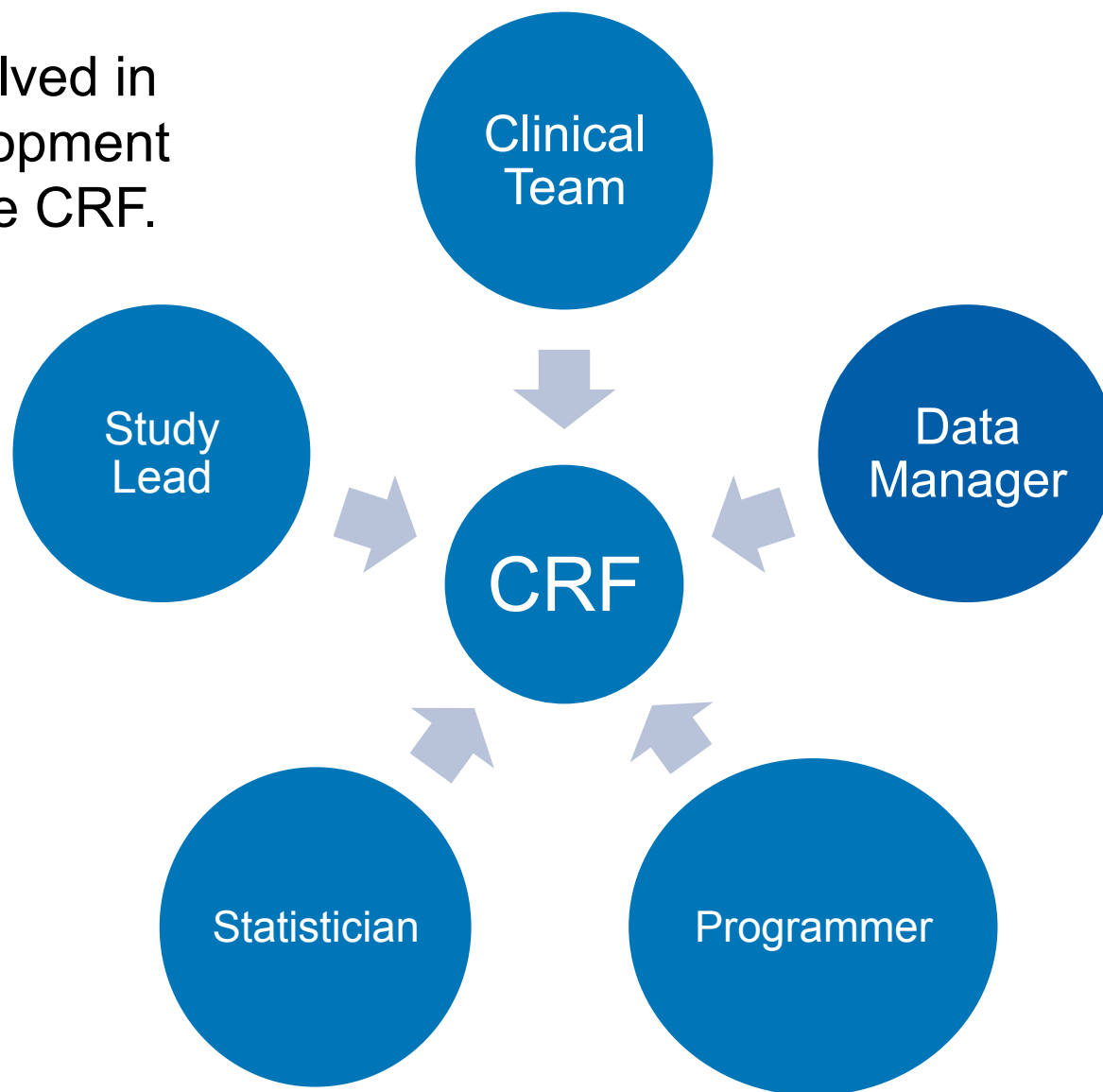
4. Real study case

5. Guidance for statistical programmers

- a. Key responsibilities
- b. Guidance for a good review
- c. Advantages of using CDISC standards

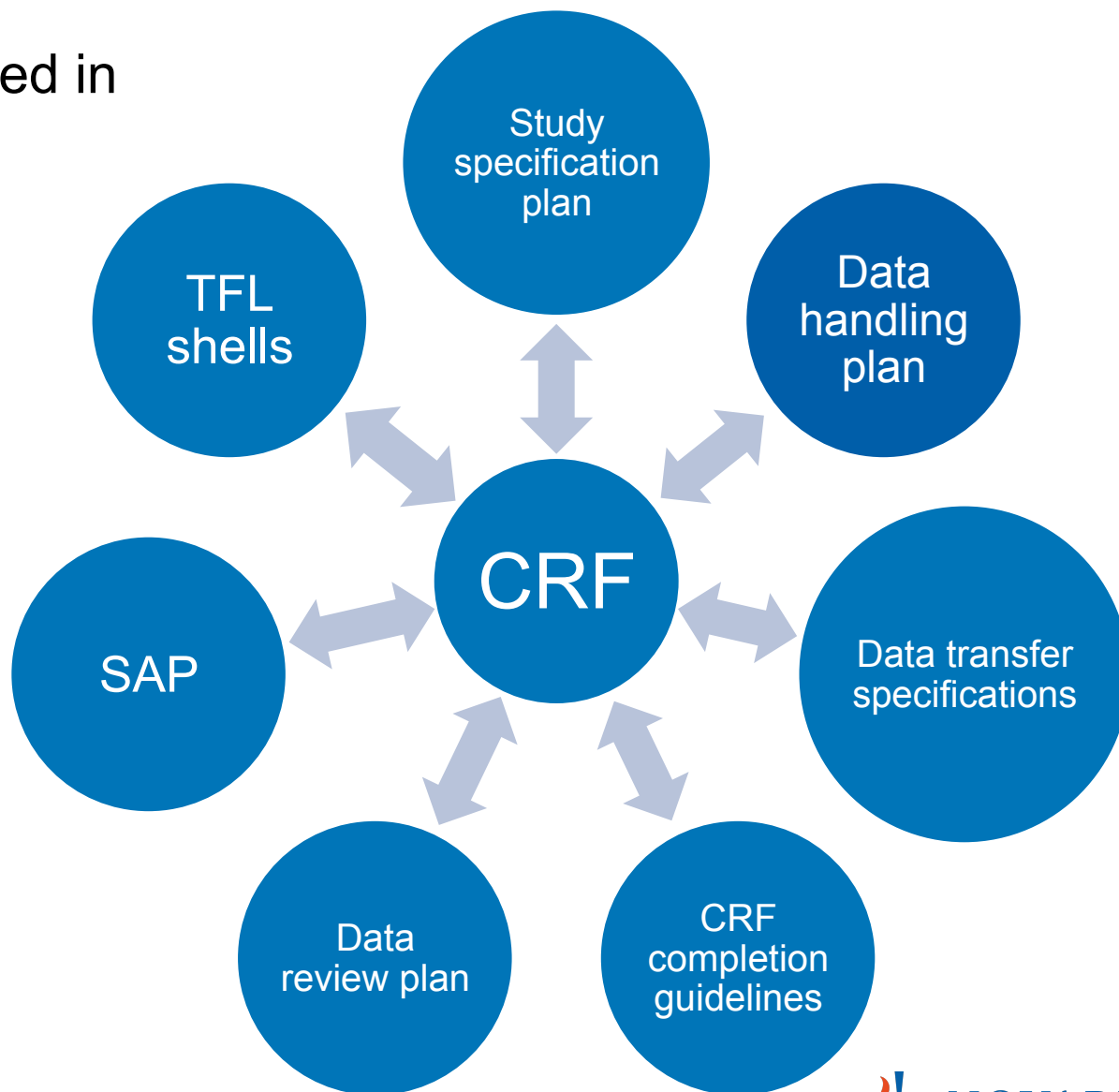
The big picture

Team / people involved in the creation, development and appraisal of the CRF.



The big picture

Documents created in parallel with CRF development.



Agenda

1. Introduction

2. Risks and consequences

3. The big picture – Clinical trial document landscape

4. Real study case

5. Guidance for statistical programmers

- a. Key responsibilities
- b. Guidance for a good review
- c. Advantages of using CDISC standards

Real Study case

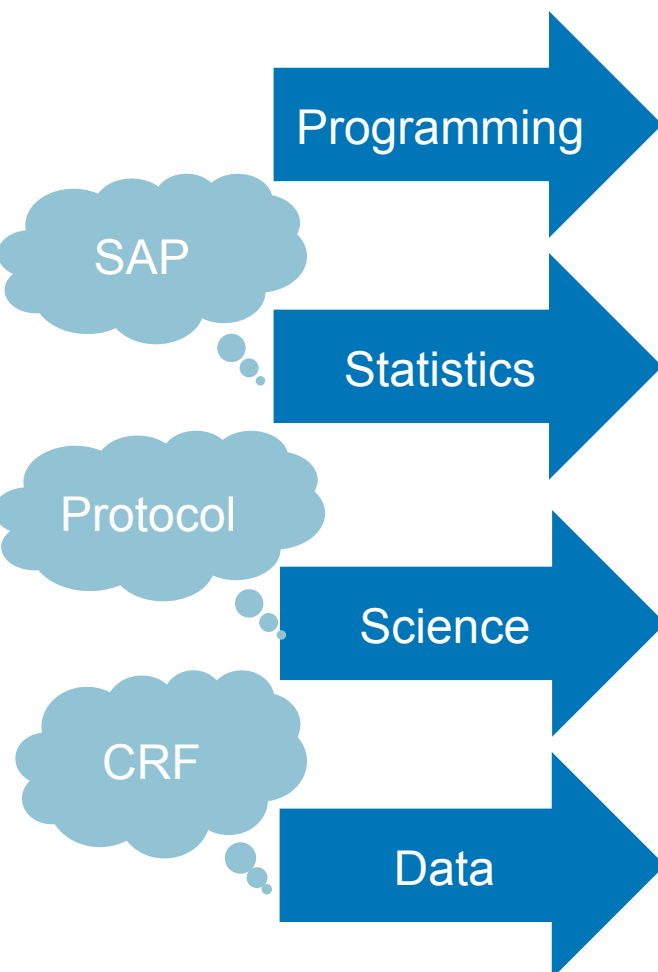


Table 14.2-1.13 Summary statistics of 6MWD (meter), by visit window

Full analysis set

Visit window	BYM338 10mg/kg (N=xxx)			BYM338 3mg/kg (N=xxx)			BYM338 1mg/kg (N=xxx)			Placebo (N=xxx)		
Statistic	Base	Post	Change	Base	Post	Change	Base	Post	Change	Base	Post	Change
Baseline												
n	Xxx			xxx			xxx			xxx		
Mean	xxx.x			xxx.x			xxx.x			xxx.x		
SD	xxx.xx			xxx.xx			xxx.xx			xxx.xx		
Minimum	xxx			xxx			xxx			xxx		
Q1	xxx.x			xxx.x			xxx.x			xxx.x		
Median	xxx.x			xxx.x			xxx.x			xxx.x		
Q3	xxx.x			xxx.x			xxx.x			xxx.x		
Maximum	xxx			xxx			xxx			xxx		
Week 8												
n	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Minimum	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Q1	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Q3	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Week 16												
...												

6MWD = 6 Minutes Walking Distance, SD = standard deviation.

Base = Baseline, Post = Post-baseline, Change = Post-baseline - baseline.

At each visit, only subjects with a value at both baseline and the post-baseline visit are included.

Baseline is defined as the last assessment before the first dose of study drug.

Real Study case

- From the protocol:

The primary objective is to demonstrate that at least one dose regimen of treatment xxx in ambulatory sporadic inclusion body myositis (sIBM) patients will increase the distance traveled as measured by change from baseline at week 52 of the 6 minute walking distance test relative to placebo. The 6 Minute Walking Distance test is done as following: the results of each test are recorded into an electronic device, including the physical length of the course, the number of completed laps that the subject walked during the test, and the distance of any non-completed lap by the subject during the test. The electronic device will calculate the total distance walked in meters. In table 1, the schedule visit assessments are described.

EPOCH	SCREENING		TREATMENT														
Visit name/ study week	Screening	BL	Day1	Wk2	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48	Wk52/ EoT
Day	-28 to -6	-5 to -1	1	15	29	57	85	113	141	169	197	225	253	281	309	337	365
6 minute Walking Test	X	X				X		X		X		X		X		X	X

Real Study case

- From SAP:

2

1

3

The primary variable is the change from baseline to Week 52 in 6 minute walking distance (6MWD), measured in meters. If a subject was present but did not perform the test at a visit because the subject was physically incapable of performing the test the result of the 6MWD will be set to zero meters. Here the physical incapability of performing the test is considered the clinical outcome of the test rather than as missing data.

- With this information, I know what I need to derive the primary endpoint as described in the SAP:

3

1. Determine baseline (BL) and week 52 (W52) assessments
2. Retrieve total distance walked
3. Determine reason not done so the rule about incapable patients can be applied

Real Study case

	ID		SCREENING Visit Name
	Center No.	Subject No.	

Six Minute Walk Test

Date of assessment DD-MON-YYYY

Time of assessment 24-hr clock

Length of a complete lap		m
Number of laps		
Additional distance		m
Total distance walked		m

If the subject did not perform the test, specify the reason

☐ Incapable
☐ Capable, but refuses
☐ Capable, but does not understand the instruction

1. Determine BL and W52 assessments
2. Retrieve total distance walked
3. Determine reason not done

ZW12I01

Epoch Document Number Subevent# Page Number 53.1

Verified ☐ Approved ☐ Locked ☐ Frozen ☐ Page Name 6 MIN WALK TEST-BASELINE Status Version

Agenda

1. Introduction

2. Risks and consequences

3. The big picture – Clinical trial document landscape

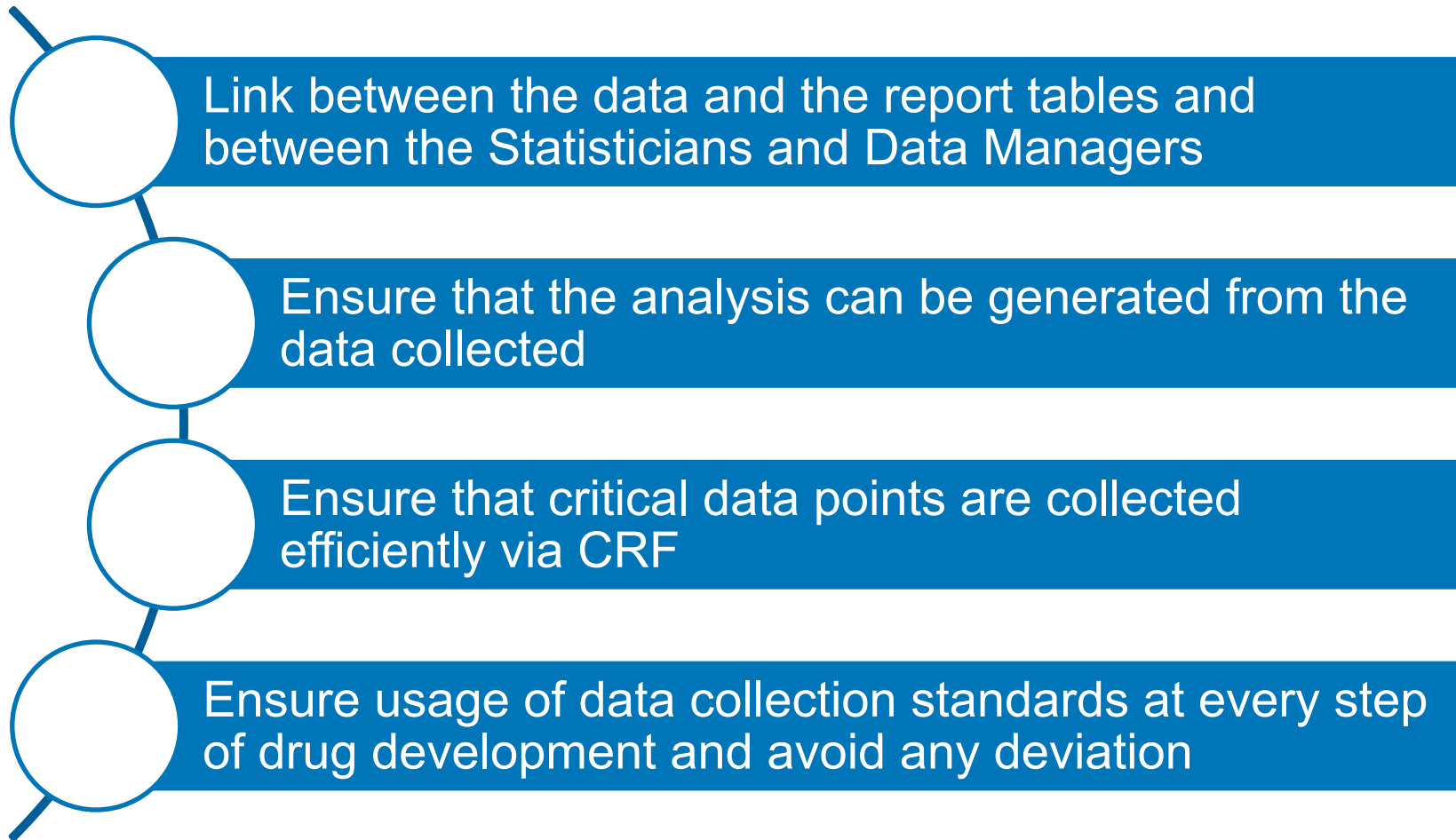
4. Real study case

5. Guidance for statistical programmers

- a. Key responsibilities
- b. Guidance for a good review
- c. Advantages of using CDISC standards

Guidance for statistical programmers

Key Responsibilities



Guidance for statistical programmers

Check list

CONSIDER

Datasets that would be created from the CRF page

Differences from previous studies before relaxing any such reviews

ENSURE

Alignment with therapeutic areas specificities

Collected data can be easily usable by their programs to generate programming requirements

Collected data answer the protocol questions and satisfy the analysis requirements

Consistency across associated documents such as non-CRF data collection specifications or data management plan

CHECK

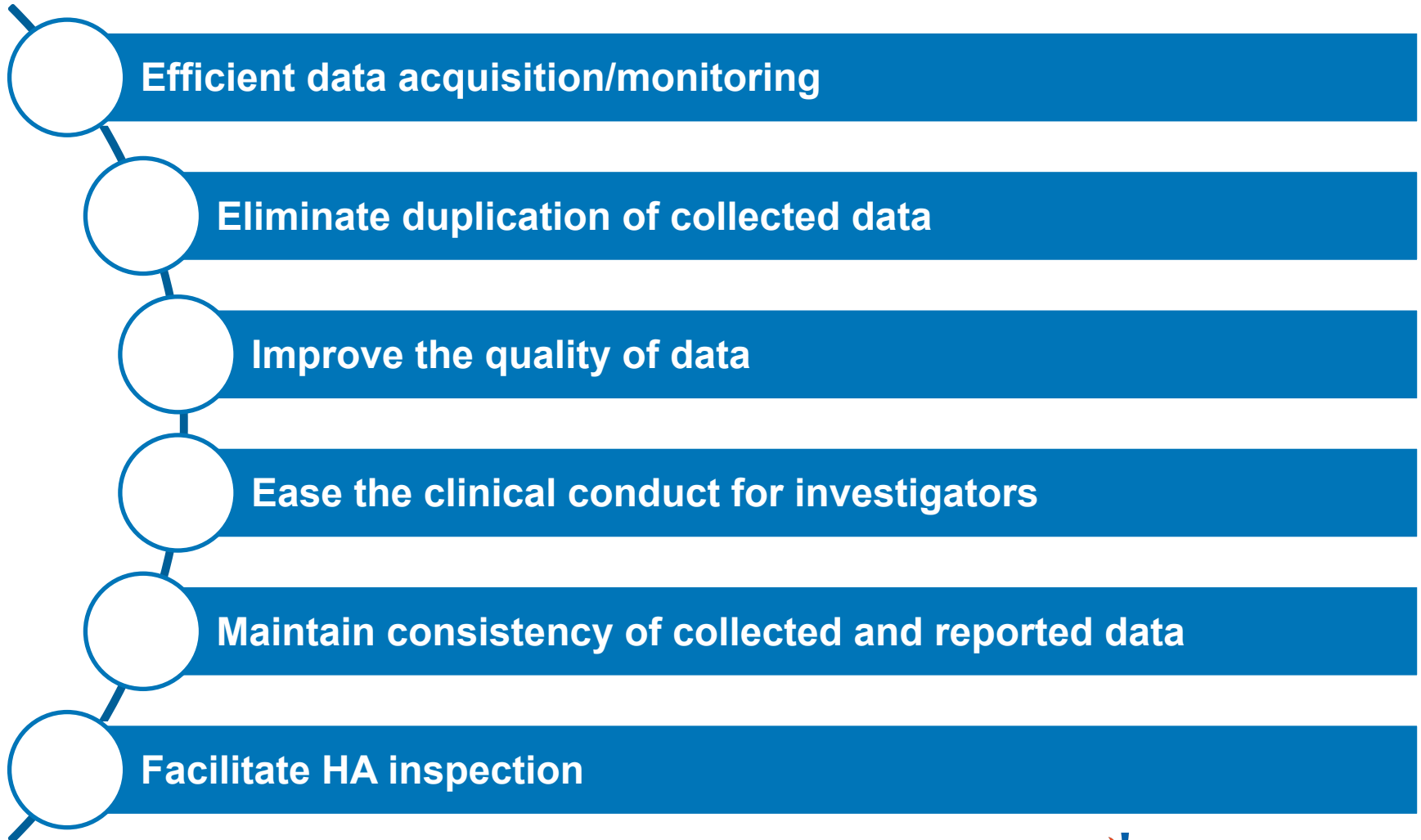
Page layout: if the instance/fields that can affect the dataset structure

Variables names have not more than 8 characters (HA requirement)

All collected fields have a controlled terminology associated

Guidance for statistical programmers

Advantages of using CDISC standards



Conclusion



The CRF review is a process where statistical programmers should be involved at an early stage

The CRF review requires a collaborative team effort

The CRF design is critical for the capture and subsequent analysis of subject clinical trial data

Seamless flow to analysis thanks to accurate and high quality clinical documentation

Conclusion



CONTACT INFORMATION

Elsa Lozachmeur
NOVARTIS Pharma AG
Work Phone: + 41 6 132 40 110
Email: elsa.lozachmeur@novartis.com

Thank you