An operation and validation process of analysis result in companion diagnostics development.

December 3, 2015

Biostatistics Department
A2 Healthcare Corporation

Takuma Ishihara

Agenda

- Overview
- Case example in the diagnostic drug development
- A general operation and validation processes in statistical analysis of clinical trial
- Future work
- Discussion

Overview

- In the trials developing companion diagnostics or such as evaluating biomarker, there is a case needs to handle a huge number of variables and several statistical approaches.

- In this case, it is may not efficient to apply a validation method commonly used such as the double programming.

Overview

- **We will introduce our quality control and operation processes for the trial of developing companion diagnostics or biomarker research.**

Case example in the diagnostic drug development

- **Selecting biomarker from a large number of candidates**
  - To predict to be the responder

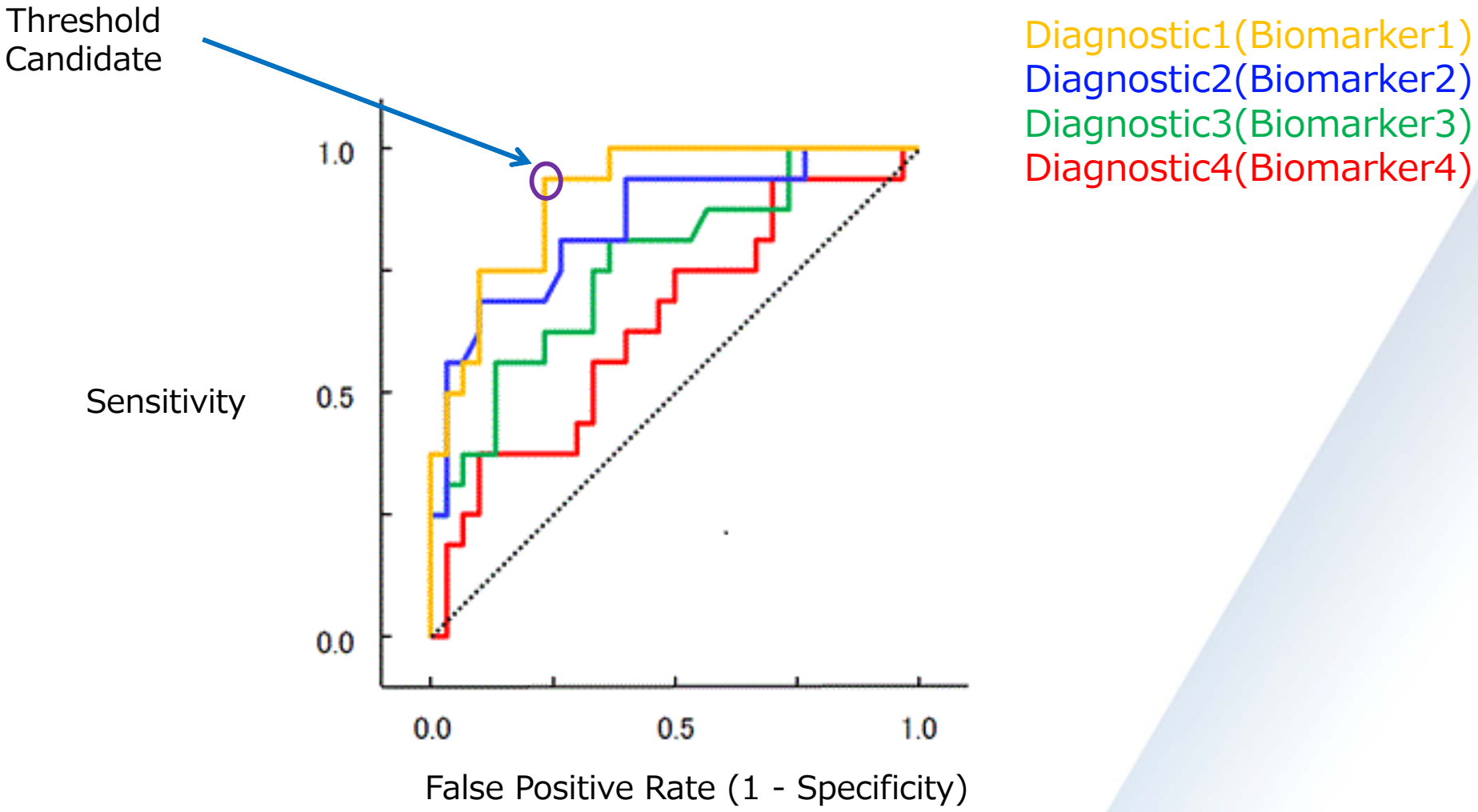
    ⇒Describing the ROC and calculating the AUC value
  - In evaluating performance of biomarkers

    ⇒Cross validation

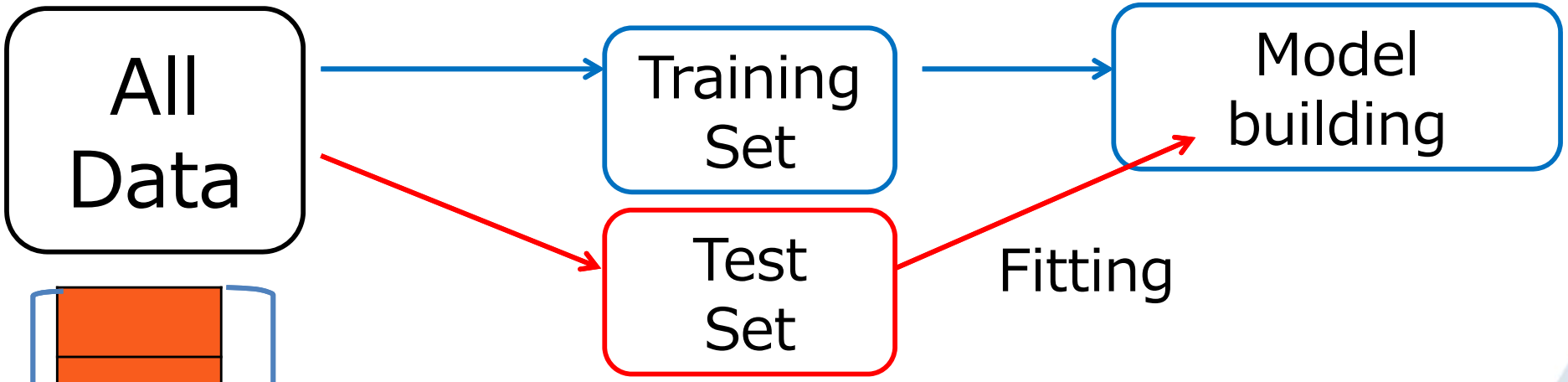
  (Model building in a training set and fitting a test set)

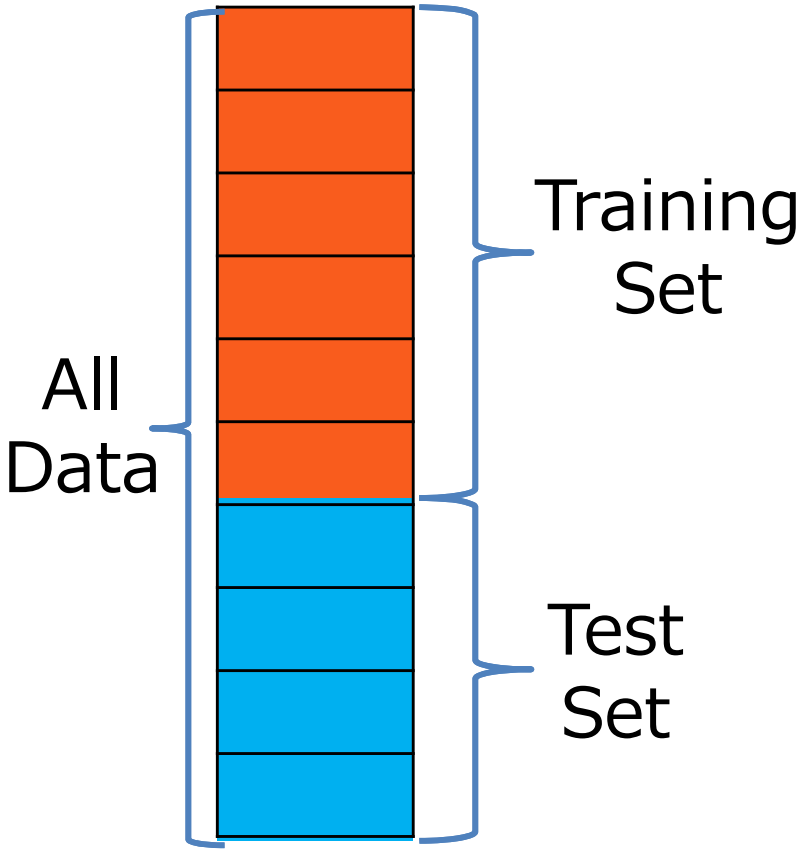
  ⇒Do simulation 100~1000 times and more
- **Selecting threshold**
  - Get the appropriate threshold from ROC
- **Multivariate analysis**
  - Analyzed using a multiple of biomarker

ROC（Receiver Operating characteristic Curve)



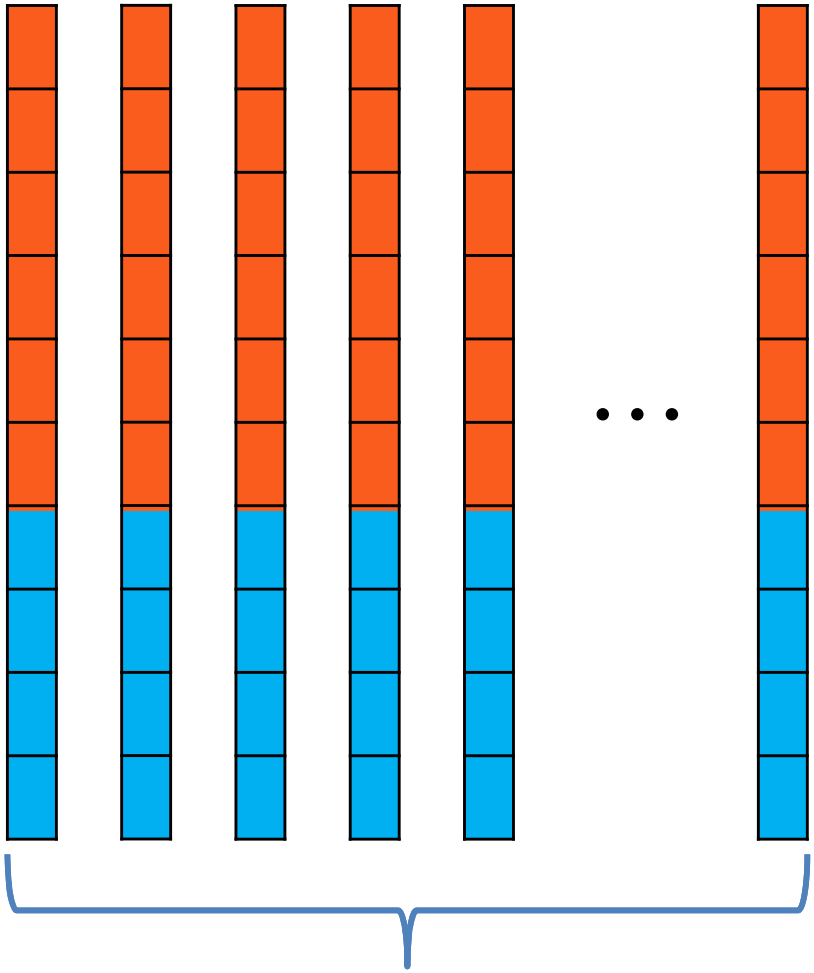
Cross Validation





For example, all data split 6 : 4 used by random number

Simulation



100 ～ 1000 times and more

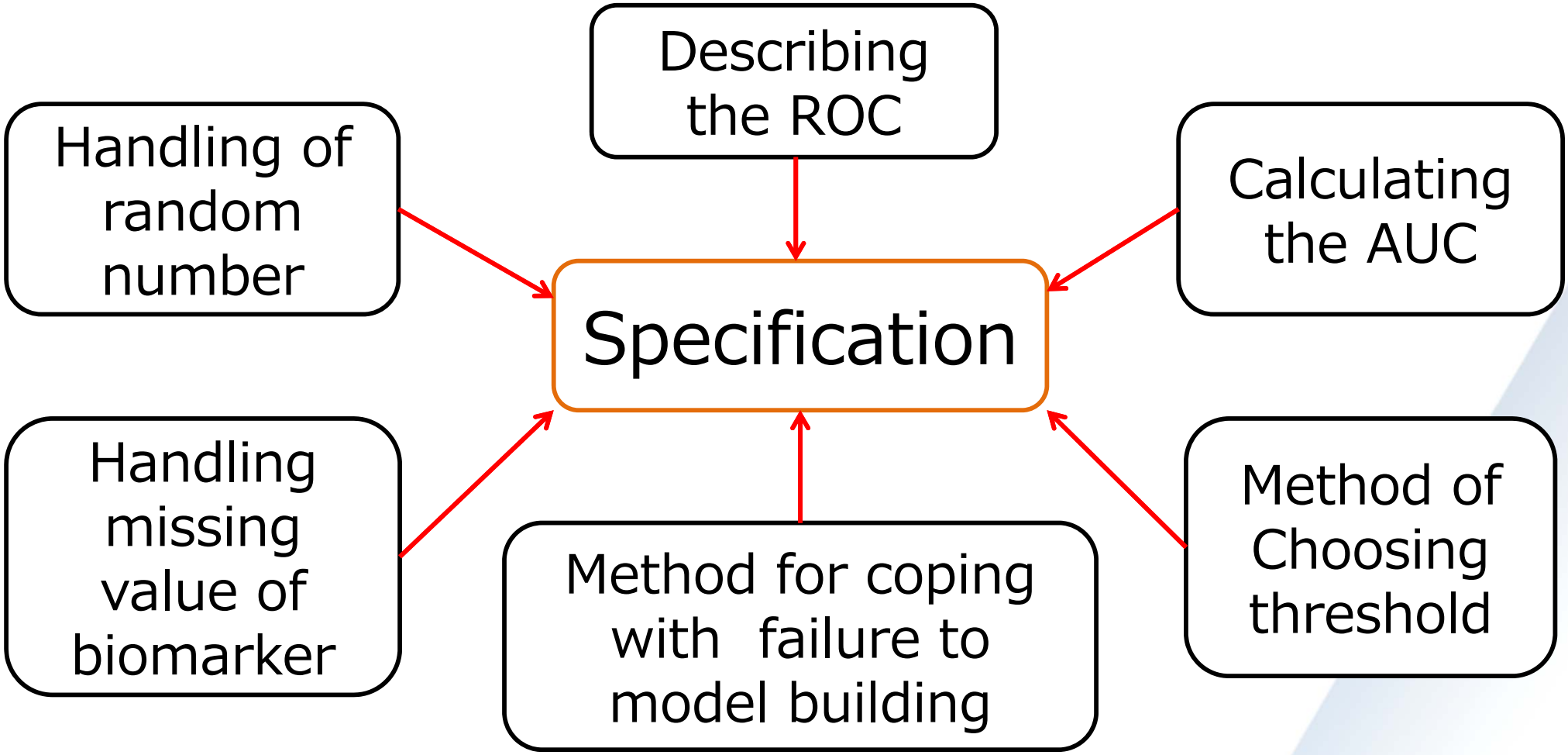
- **Evaluating performance of biomarkers**

・Threshold is established in Training set.

⇒Calculating sensitivity and specificity by test set.

Treat a large number of biomarker candidates.

Drawing up a specification



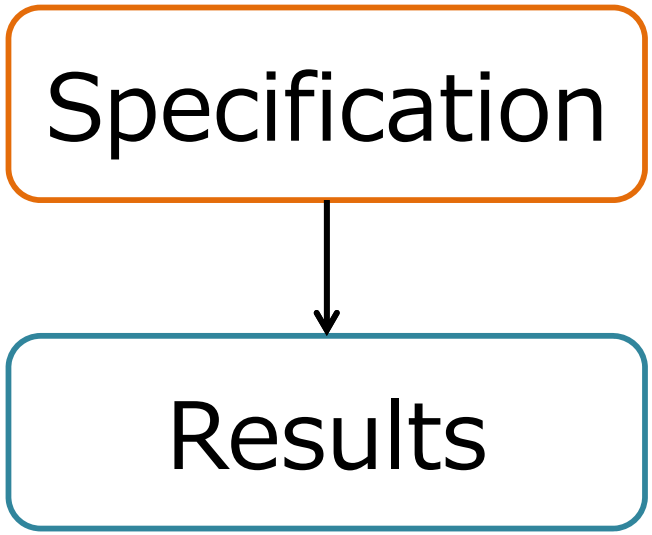
Output a result

- **The way of using a random number in statistical programming**
- **Model building in a training set and fitting a test set**
  - ・When the test set and training set are provided , there is the case the test(training) set includes only the patients who are responder(non-responder)
  - ・Handling missing value of biomarker
- **Choosing the value of threshold**

Output a result

ex) programmers can clearly understand the specification.

Programming

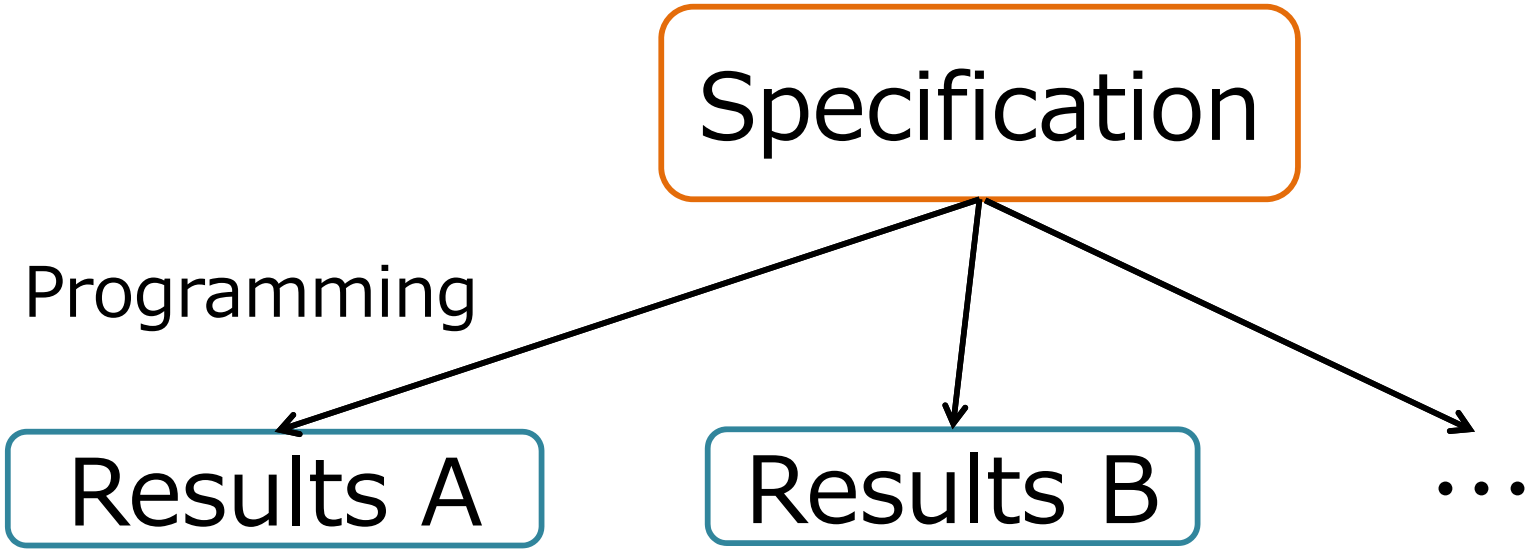


Sensitivity and Specificity in Test Set

Treatment Group	Efficacy Parameter	BM Name	Sensitivity						
			Mean	SD	95%CI (Lower)	95%CI (Upper)	Q1	Median	Q3
Group1	Parameter1	AAAA	0.511	0.192	0.373	0.649	0.333	0.536	0.667
Group1	Parameter1	BBBB	0.343	0.222	0.184	0.502	0.25	0.268	0.5
Group1	Parameter1	CCCC	0.597	0.248	0.406	0.787	0.5	0.625	0.75

Output a result

ex) programmers can not clearly understand the specification.



Sensitivity and Specificity in Test Set

Treatment Group	Efficacy Parameter	BM Name	Sensitivity						
			Mean	SD	95%CI (Lower)	95%CI (Upper)	Q1	Median	Q3
Group1	Parameter1	AAAA	0.511	0.192	0.373	0.649	0.333	0.536	0.667
Group1	Parameter1	BBBB	0.343	0.222	0.184	0.502	0.25	0.268	0.5
Group1	Parameter1	CCCC	0.597	0.248	0.406	0.787	0.5	0.625	0.75

Sensitivity and Specificity in Test Set

Treatment Group	Efficacy Parameter	BM Name	Sensitivity						
			Mean	SD	95%CI (Lower)	95%CI (Upper)	Q1	Median	Q3
Group1	Parameter1	AAAA	0.537	0.224	0.377	0.698	0.286	0.586	0.714
Group1	Parameter1	BBBB	0.343	0.222	0.184	0.502	0.25	0.268	0.5
Group1	Parameter1	CCCC	0.597	0.248	0.406	0.787	0.5	0.625	0.75

・・・

General validation method

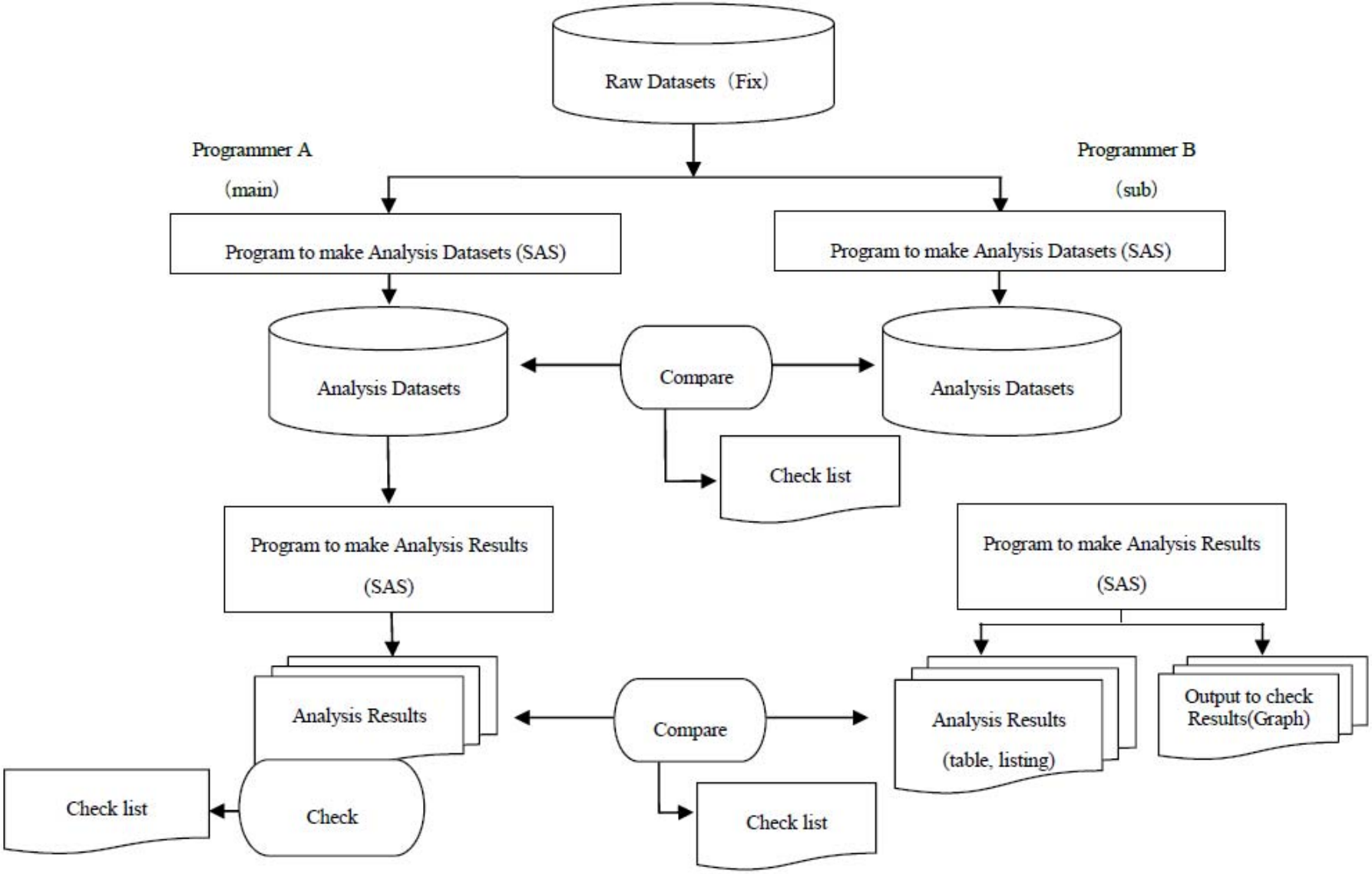
Double programming

The validation method to detect errors in programming.

Programmers A and B code a program independently.

To detect a mistake by matching both the results.

Validation process using a double programming



The result of the comparison (Double programming)

Where is the cause?

Analysis results(main)

Sensitivity and Specificity in Test Set

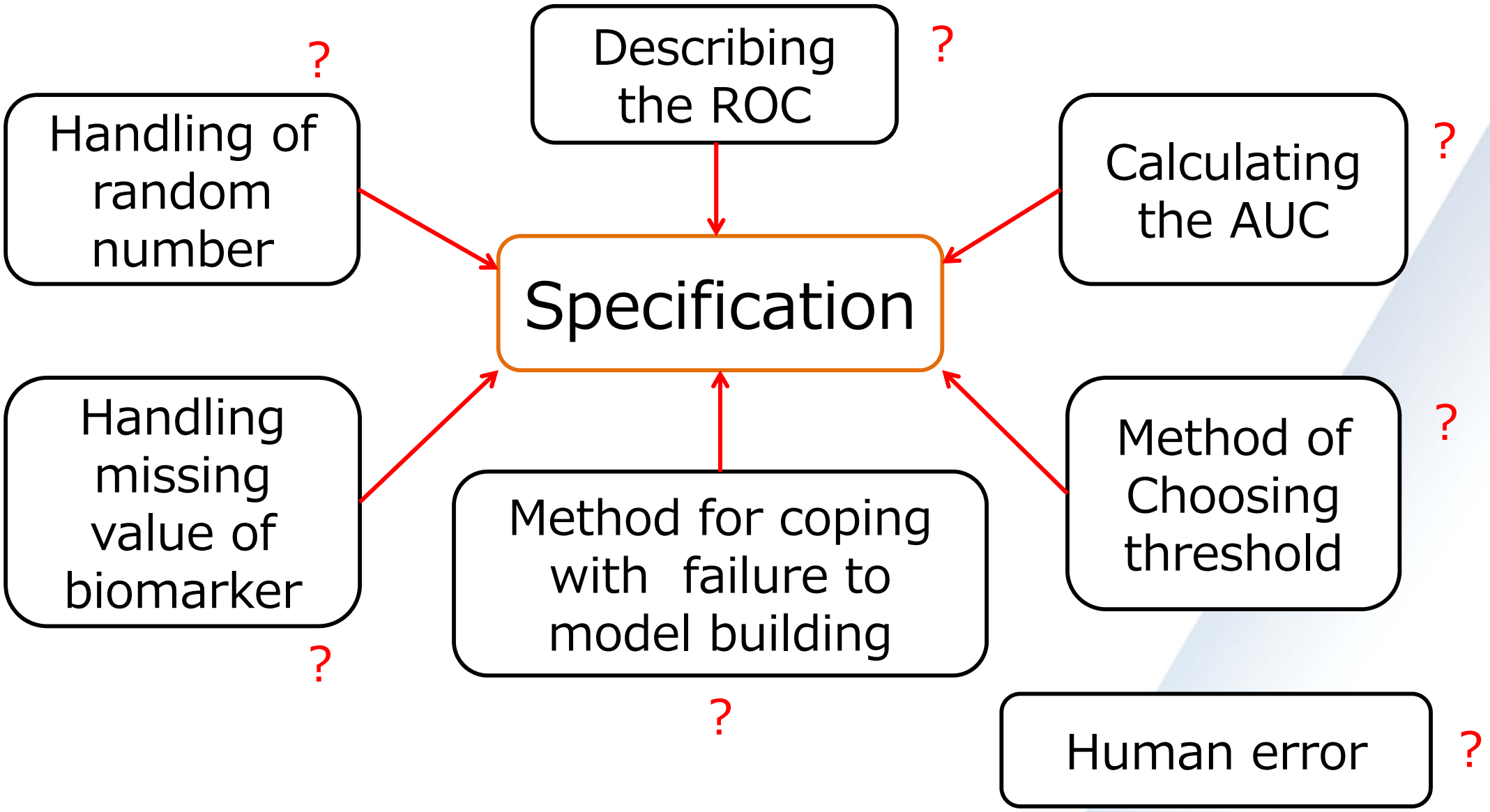
Treatment Group	Efficacy Parameter	BM Name	Sensitivity						
			Mean	SD	95%CI (Lower)	95%CI (Upper)	Q1	Median	Q3
Group1	Parameter1	AAAA	0.511	0.192	0.373	0.649	0.333	0.536	0.667
Group1	Parameter1	BBBB	0.343	0.222	0.184	0.502	0.25	0.268	0.5
Group1	Parameter1	CCCC	0.597	0.248	0.406	0.787	0.5	0.625	0.75

Analysis results(sub)

Sensitivity and Specificity in Test Set

Treatment Group	Efficacy Parameter	BM Name	Sensitivity						
			Mean	SD	95%CI (Lower)	95%CI (Upper)	Q1	Median	Q3
Group1	Parameter1	AAAA	0.537	0.224	0.377	0.698	0.286	0.586	0.714
Group1	Parameter1	BBBB	0.343	0.222	0.184	0.502	0.25	0.268	0.5
Group1	Parameter1	CCCC	0.597	0.248	0.406	0.787	0.5	0.625	0.75

Where is the Cause?



In a case that the double programming is effective

Double programming

This method is said to be effective when programmers can clearly understand the specification and generate the exactly same results by following the same specification.

In this example it is not the case
need to shape creating situation describing above.

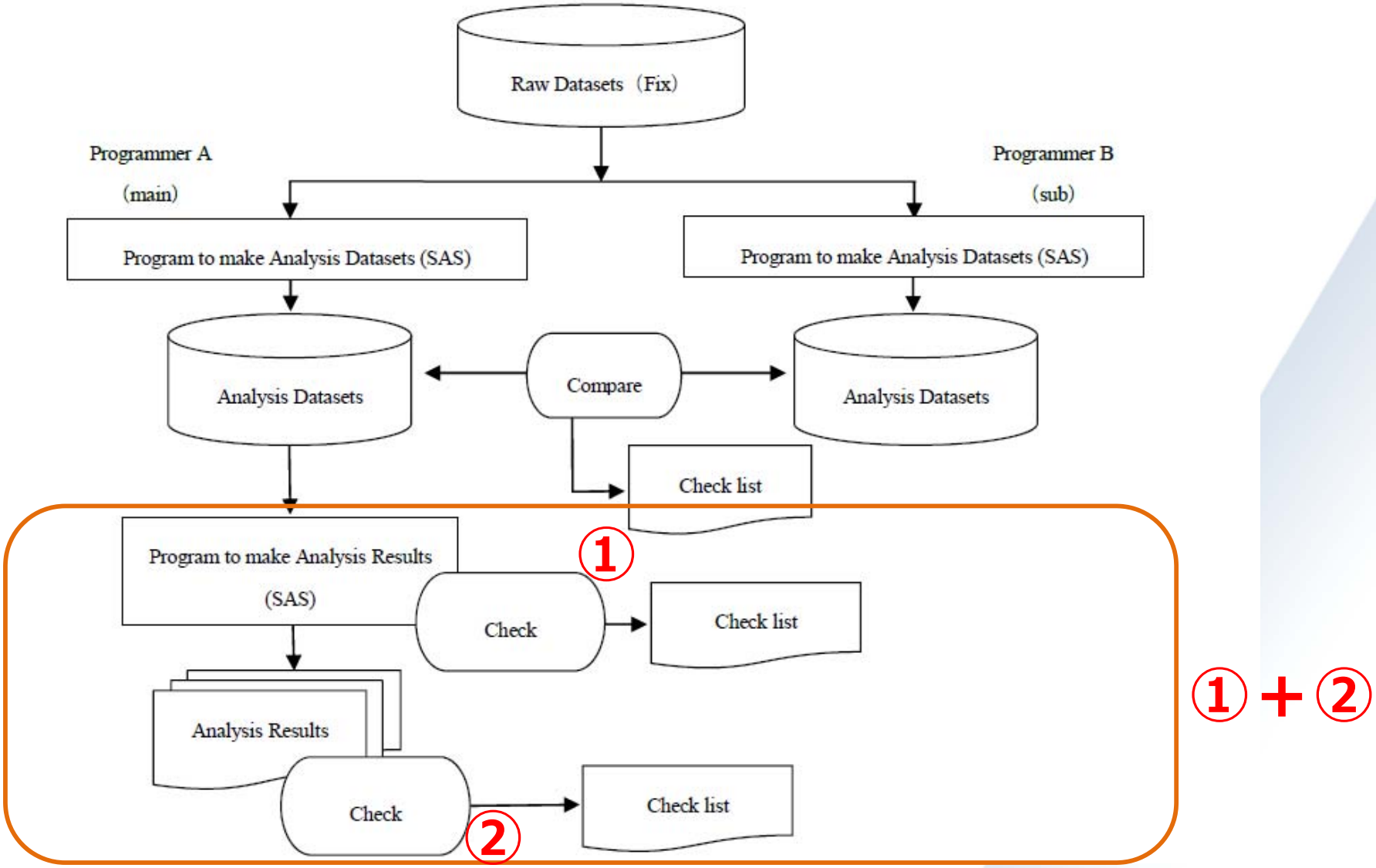
Therefore, we have followed a different process.

Validation process

We have managed single programming process rather than adapt to the situation to take validate in double programing.

Considering how to take the validation based on check the contents of a single program one by one.

Validation process of single programming and white check



Method ① : Check of the program

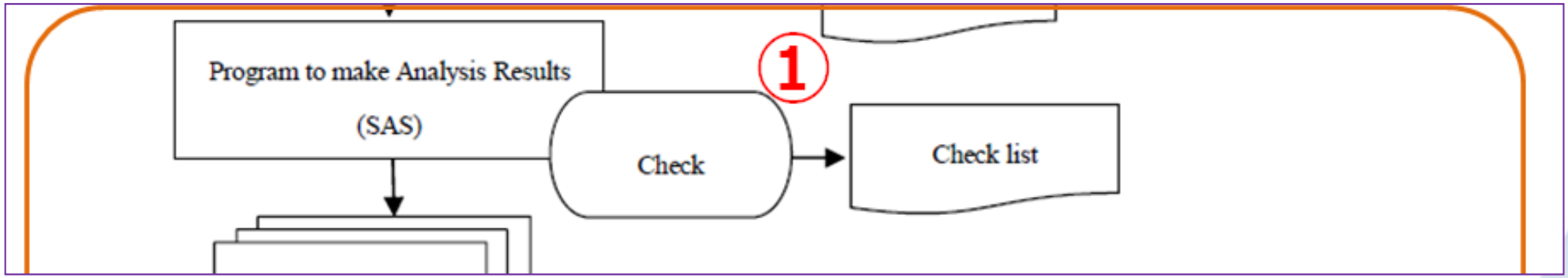
【Purpose】

To ensure that the logic is correctly reflected and perform in the program.

【Operating procedures】

1. To code the program by single.
2. Hold a meeting for reviewing program code. To review contents of program, data structure and output of results one by one.
3. Printing program code, and marking points checked. If modification is required redlining to that point.
4. To modify the program and repeating 1 to 3.
5. To record the date of checking and cording program to the list.

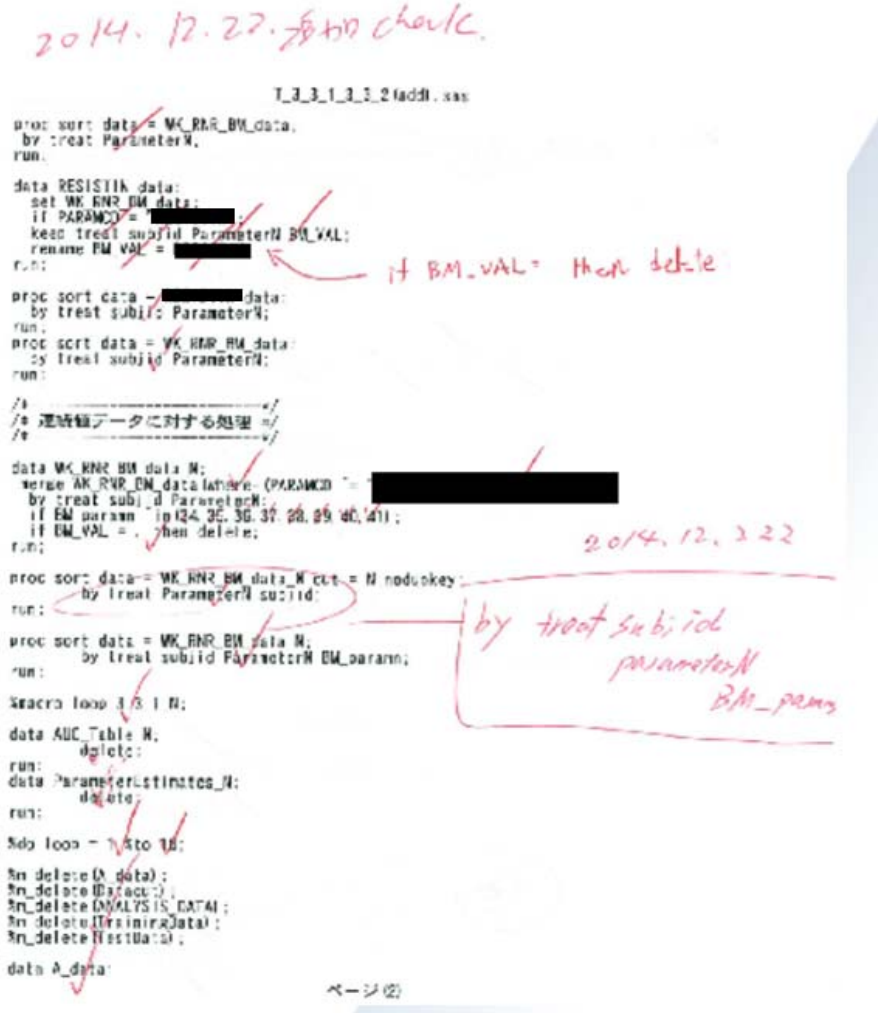
Method ① : Check of the program



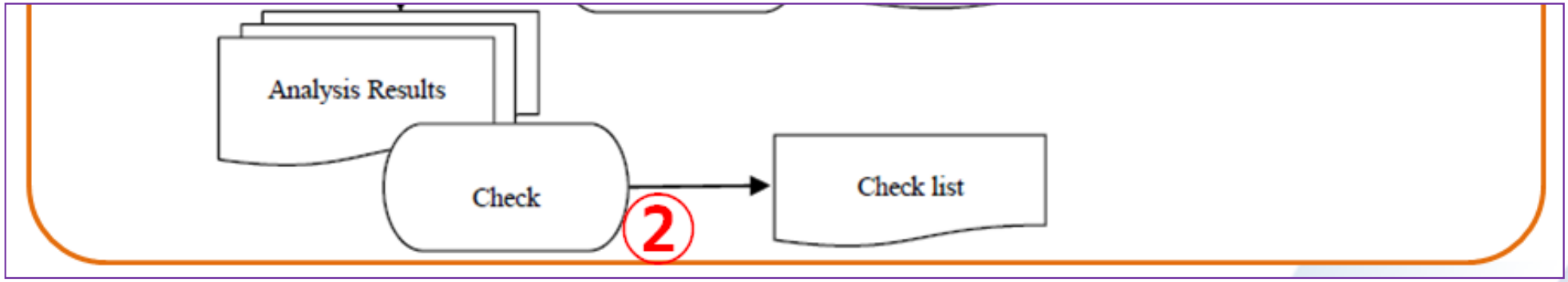
- **Check of the program**
  - **・Hold a meeting for reviewing**

- **Participant in a conference**
  - Programmer
  - Reviewer(More than one person)
  - Reporter

Method ① : Check of the program(recording media)



Method ② : Check of analysis results



- **Check of results**
  - ・Check results of random sampling

Method ②　: Check of analysis results

【Purpose】

To check the validity of analysis results.

【Operating procedures】

1. To extract several analysis results at random.
2. To put the extracted results into print and check the results with red pen.
3. To record the date checked on the checklist.

Future work

- To specify the situations in which single programming can be useful.
- To choose a suitable validation process corresponding to each analysis result.

Discussion

- We introduced our quality control and operation processes in handling a huge number of variables and several statistical approaches using single programming.
- In some cases, double programming may useful.

- Therefore, we should choose a validation process in consideration of the benefits of both single and double programming as well as combine them as needed.