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**General note:**

This document is based on the template for a Software Development Planning, as proposed in the IEC 62304:2006, Section 5.1.

In order to prevent deviations from this template all chapters and paragraphs are displayed. When a chapter or paragraph is not applicable to the subject described in this Software Development Planning, this will be recorded as NA.

# Introduction

The purpose of this plan is to lay-out the activities and deliverables for the development of the R-package DASCOMBAT, that will be used as part of the data analysis software for IOpener IVD products, including PRO7602 (for IOpener-melanoma) and PRO7603 (for IOpener-NSCLC). The purpose of this software development plan is to establish the safety and effectiveness of using the R PACKAGE DASCOMBAT for the data analysis diagnostic measurements.

This plan, and related documents, will document the intended use of the software and establish the safety and effectiveness of using the software without causing any unacceptable risks.

DASCOMBAT is an R-package that is used to adjust for batch effects in microarray datasets where the batch covariate is known, using methodology described in Johnson et al. 2007. It uses an empirical Bayes frameworks for adjusting data for batch effects. Users are returned a data set that has been corrected for batch effects. The input data are assumed to be cleaned and normalized before batch effect removal.

The R-package DASCOMBAT is used as a resource for modules that perform normalization in the data analysis pipelines for IOpener products, including the product specific modules DASNORMALIZE-IOMEL in PRO7602 and DASNORMALIZE-IONSCLC in PRO7603.

Hence, the R-package DASCOMBAT will be used for the purpose of calculating a batch correction between known and indicated batches using the ComBat methodology. The DASCOMBAT R-package is executed in the R environment and implements the following:

* Receives suitably normalized kinase activity measurement profiles and a batch indicator variable.
* Calculates a ComBat correction model for batch effects in the measurement profiles based on the batch indicator variable, see below for details on the calculation method.
* Returns the ComBat correction model.
* Applies the ComBat correction model to input data and returns the corrected data. The input data can be the same data that was used to calculate the model, new data from the same batches as the data that was used to calculate the model (i.e REF and DAS samples), or a combination thereof. DAS-OMBAT implements the option to use an indicated *reference batch* in the correction. The reference batch will be unchanged and the other batches changed towards the reference batch.
* DASCOMBAT implements the option to calculate a Location-only (mean-only) model or a Location-Scale model.
* In the original ComBat methodology the option exist to use additional covariates besides the batch indicator variable. This option will not be implemented.

# Scope

Ther scope of this document istThe software development plan of the R-package DASCOMBAT

## Out of scope

The DAS platform legacy software (which is covered in FRM-6313) is out of scope.

DASCOMBAT will be used as a resource for normalization steps implemented in the data analysis pipelines for IOpener IVD products (such as DASNORMALIZE\_IOMEL and DASNORMALIZE\_IONSCLC) and will not be independently integrated to the DAS platform. DASNORMALIZE-IOMEL and DASNORMALIZE-IONSCLC are defined separately and are out of scope for this plan.

## Software Safety Classification

[Define the overall classification of the software (Class A, B or C). Also, document the justification for this classification]

The module is a critical module for preprocessing DAS results prior to calculating a diagnostic result.

Incorrect functioning of the DASCOMBAT module can result in an incorrect diagnostic result. Therefore, the initial risk classification of the software is class C.

Subsequently, risks will be further assessed using the Risk Management Process applied as part of the design and development of the applicable IOpener product according to SOP7350 – Design and Development and SOP4500 Risk Management. This includes a performing a FMEA on DASCOMBAT.

# Roles and responsibilities

[Define Roles and Responsibilities for the Software Development Plan and the overall project]

PM (Project Manager Rik de Wijn

PO (Product Owner) Laken Woods

ST (Software Team) Faris Naji, Alexandre Maurel, Rik de Wijn

The responsibilities are outlined in SOP 6300 Software Planning Process.

# Reference Documents

## System references

### *System Requirements*

[Include a reference to the system requirements of the medical device. These will be used as input for the software requirements.]

The DASCOMBAT module is an R-package that operates in the R environment. It supplies functions that can be called from the R environment.

The measurements or phosphorylation profiles are represented as a matrix of measurements where each column represents an observation (e.g. array, Sample name, Patient ID) and each row represents a particular peptide in the phosphorylation measurement. The batches are represented by a batch indicator variable that contains a batch identifier for each observation in the measurement data.

The ComBat method is described in literature by Johnson et al. [1] and Zhang et al. [2] and is implemented in its original form in the R-package SVA [3]. However, the SVA package cannot be used “as is” because a modification is necessary to allow a correction calculated on a set of REF samples to be applied to a set of DAS samples, as described in [4]. Therefore, the R-Package DASCOMBAT will be programmed for this purpose, using the information in Appendix A (210228RW19030 Appendix A methodology-combat ) and appendix B of [4] as supporting documentation.

The full specification process for the DASCOMBAT module is outlined by the SOP6300 software development. However, the DASCOMBAT module is a low complexity module performing a single task. The software is intended to run on a dedicated generic Windows PC. Therefore, the module DASCOMBAT is fully specified in the requirements document:

* dascombat\_6305-Software Requirements.docx

, and a dedicated architecture document and detailed design document are deemed unnecessary.

## DevelopmentStandards, Methods and Tools and Regulatory references

### Standards

[List here or include references to standards used in development of the software]

* IEC 62304:2006
* ISO13485
* ISO14971

This standard refers to the Medical device software -- Software life cycle processes.

### Methods

[List here or include references to methods used in development of the software]

Methods for software development are covered in SOP6300 and the underlying WI6302 – Sofware Coding Guidleine

### Tools

[List here or include references to tools used in development of the software. Development tools can also be included in the SOUP Configuration Items List]

The development tools are outlined in the soup configuration list in section 10.

[Refer to the SOUP items list with the way how to identify the development tools in that list]

### Regulatory references

[List here or include references to relevant regulations used in development of the software]

* EU Directive 98/79/EC - ln Vitro Diagnostic Medical Devices Directive
* EU Regulation 2017/746 - ln Vitro Diagnostic Medical Devices Regulation

# Processes used in the development

The following processes will be used during the development of the medical device software (version updated to Dec-2024)

|  |  |  |
| --- | --- | --- |
| **Document ID** | **Title** | **Version** |
| SOP 6300 | Software Development | 2.0 |
| SOP6306 | Software Maintenance | 2.0 |
| SOP6309 | Software configuration management | 1.2 |
| SOP 4500 | Risk Management Process | 2.0 |
| SOP 4300 | Change Control | 3.1 |
| SOP4600 | Validation of Computer Software used for production and QMS | 1.2 |
| SOP7350 | Design and Development | 1.1 |

# Software Deliverables

[Provide a list of the outcome of this development process. These should be all the software, it’s components and other items that are created to operate directly or indirectly with the medical device. This can also be provided in the Software Configuration List. In that case this section can be removed]

* DASCOMBAT (R-package)

The R-package is the software product. A software git repository is delivered and located at:

https://github.com/pamgene/dascombat

The software repository contains all the code, tests and documentation, unless otherwise specified.

# Traceability

The traceability matrix provides the overview of relationships between the system requirements, software requirements, test results and risk control measures within the software. This matrix shows all the specified requirements have been addressed, tested. It includes the list of implemented risk control measures.

The documents outlining traceability are:

* Dascombat-6301-Traceability Matrix.xlsx

# Software Configuration List

To keep an overview of the software configuration of all DAS modules a separate common repo called DASCOMMON is used, this will also highlight any potential conflicts between SOUP or DAS modules.

The document outlining configuration is:

180601-6302 Software Configuration List.xlsx

Located at:

<https://github.com/pamgene/dascommon/tree/master/docs>

# SOUP Configuration Items

To keep an overview of the software configuration of all DAS modules a separate common repo called DASCOMMON is used, this will also highlight any potential conflicts between SOUP or DAS modules.

The document outlining SOUP is:

180601-6303 SOUP configuration items.xlsx

Located at:

<https://github.com/pamgene/dascommon/tree/master/docs>

# Software Testing Plan

Software testing will be performed as outlined in SOP6300 Software Development

The testing of DASCOMBAT is performed at the unit test level. The integration and system testing is considered not applicable, as this model is a resource for the DASNORMALIZE modules, and will not be independently integrated with the DAS-PLATFORM.

Integration and system testing of this module will be performed as part of the integration and system testing of DASNORMALIZE-IOMEL and DASNORMALIZE-IONSCLC

# Software risk management

The software risk management conducts the activities and tasks of the software risk management process, including the management risks related to SOUP*.*

Risk management is performed according to SOP4500 as part of the risk management activities for METHOD DAS as specified in:

* 210200KS18001 Risk Management Plan METHOD DAS
* 210227RW18038 Risk Management DAS software.

The specific implementation of the R-package DASCOMBAT will be done by implementing it in the applicable DAS module such as DASNORMALIZE-IOMEL and DASNORMALIZE\_IONSCLC. Therefore, the risks associated with using it in the DAS process (e.g. risks associated with correctness of input data, correctness of settings etc.) are best handled in the risk analysis to be performed for these modules..

For DASCOMBAT a FMEA was performed focussing on correct implementation of the COMBAT methodology:

* DASCOMBAT-FRM4503-FMEA sheet.xlsx

14 risks were identified which are addressed by software testing.

# Project deliverables

| **Document ID** | **Document name** |
| --- | --- |
| 210227RW20010 | Software Development plan |
| 181001-6302 | Software Configuration |
| 181001-6303 | SOUP Configuration |
| dascombat-6304-Software Requirements | Software requirements |
| dascombat-6304-Software Requirements | Traceability Matrix |
| dascombat-FRM4503-FMEA Sheet | FMEA sheet |
| Not applicable (see section 10) | Software integration testing |
| Not applicable (see section 10) | Software system testing |

# Common Software Defects

This section lists the (categories of) common software defects that have been identified in relation to the selected programming technology. For each of the items in the list it is described how these common defects can be avoided (or if not otherwise possible will be mitigated to the best possible extend).

|  |  |
| --- | --- |
| **Common Software Defect** | **Defect resolution or mitigation** |
| Interruption due to DASPLATFORM | Restart |
| Interruption due to Windows operating system | Restart |

# Definitions and abbreviations

SOUP Software of unknown provenance

SP Software Product, i.e. DASCOMBAT

DAS PLATFORM The software platform to which modules plug-in

IOpener-melanoma, IOpener-NSCLC The name of the medical device

FMEA Failure Mode and Effect Analysis

DAS Diagnostic Assay Services

REF Reference sample, used to indicate reference sample or Internal Assay Control sample.

# Appendix

Not applicable

# References and related documents

[1] W. E. Johnson, C. Li, and A. Rabinovic, “Adjusting batch effects in microarray expression data using empirical Bayes methods,” *Biostatistics*, vol. 8, no. 1, pp. 118–127, Jan. 2007.

[2] Y. Zhang, D. F. Jenkins, S. Manimaran, and W. E. Johnson, “Alternative empirical Bayes models for adjusting for batch effects in genomic studies,” *BMC Bioinformatics*, vol. 19, no. 1, p. 262, Jul. 2018.

[3] J. T. Leek *et al.*, “SVA: surrogate variable analysis.” 2020.

[4] PamGene International, “210228RW19030 Development and verification of the use of reference samples in teh DAS lab,” 2019.

# Signatures and approval

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Role** | **Function title** | **Name** | **Signature** | **Release date** |
| Author | Head of DAS | Rik de Wijn |  |  |
| Reviewer | Software Consultant | Pierick Kinif |  |  |
| Authoriser | Head of DAS | Rik de Wijn |  |  |
| Quality Assurance | QARA Manager | Anja Wiersma |  |  |

# History

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Date** | **Remarks** | **Document owner** |
| 1.0 | 01-Jan-2020 | Initial version | Faris Naji |
| 1.1 | 3-Dec-2024 | Review before finalization (following non-conformity DAS2024-NC-02) | Rik de Wijn |