Detailed workflow specification and component roadmap for high-throughput image analysis of large-scale studies

Grant agreement no.: 601055 (FP7-ICT-2011-9)
Project acronym: VPH-DARE@IT
Project title: Dementia Research Enabled by IT
Funding Scheme: Collaborative Project
Project co-ordinator: Prof. Alejandro Frangi, University of Sheffield
Tel.: +44 114 22 20153
Fax: +44 114 22 27890
E-mail: a.frangi@sheffield.ac.uk
Project web site address: http://www.vph-dare.eu

Due date of deliverable: Month 9
Actual submission date: Month 12
Start date of project: April 1st 2013
Project duration: 48 months

Work Package & Task: WP3, Task 3.1
Lead beneficiary: UCL
Editor: David M. Cash
Author(s): Nicolas Toussaint, Miklos Espak, Sébastien Ourselin
Quality reviewer: Prof. Wiro Niessen, Dr. Jyrki Lötiönen

Project co-funded by the European Union within the Seventh Framework Programme

<table>
<thead>
<tr>
<th>Dissemination level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pu</td>
</tr>
<tr>
<td>PP</td>
</tr>
<tr>
<td>RE</td>
</tr>
<tr>
<td>CO</td>
</tr>
</tbody>
</table>

Issue Record
<table>
<thead>
<tr>
<th>Version no.</th>
<th>Date</th>
<th>Author(s)</th>
<th>Reason for modification</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>13/12/'13</td>
<td>Nicolas Toussaint</td>
<td>Initial Draft</td>
<td>First draft</td>
</tr>
<tr>
<td>0.2</td>
<td>18/12/'13</td>
<td>David Cash</td>
<td>Revision to initial draft</td>
<td>Consolidate/Review</td>
</tr>
<tr>
<td>0.3</td>
<td>30/1/'14</td>
<td>Nicolas Toussaint</td>
<td>Revision ready to circulate</td>
<td>Draft/to circulate</td>
</tr>
<tr>
<td>0.4</td>
<td>17/2/'14</td>
<td>Nicolas Toussaint</td>
<td>Sheffield / corrected</td>
<td>Draft/to circulate</td>
</tr>
<tr>
<td>0.5</td>
<td>21/2/'14</td>
<td>David Cash</td>
<td>Final modifications</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>24/2/'14</td>
<td>Nicolas Toussaint</td>
<td>Final modifications</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>18/3/'14</td>
<td>Nicolas Toussaint</td>
<td>Last modifications</td>
<td>To send to project board</td>
</tr>
<tr>
<td>1.0</td>
<td>30/5/'14</td>
<td>M.A. Pullinger</td>
<td>Final PMO QC check and updating to latest deliverable template</td>
<td>Final version</td>
</tr>
</tbody>
</table>

Copyright Notice

Copyright © 2014 VPH-DARE@IT Consortium Partners. All rights reserved. VPH-DARE@IT is an FP7 Project supported by the European Union under grant agreement no. 601055. For more information on the project, its partners, and contributors please see http://www.vph-dare.eu. You are permitted to copy and distribute verbatim copies of this document, containing this copyright notice, but modifying this document is not allowed. All contents are reserved by default and may not be disclosed to third parties without the prior written consent of the VPH-DARE@IT consortium, except as mandated by the grant agreement with the European Commission, for reviewing and dissemination purposes. All trademarks and other rights on third party products mentioned in this document are acknowledged and owned by the respective holders. The information contained in this document represents the views of VPH-DARE@IT members as of the date of its publication and should not be taken as representing the view of the European Commission. The VPH-DARE@IT consortium does not guarantee that any information contained herein is error-free, or up to date, nor makes warranties, express, implied, or statutory, by publishing this document.

Author(s) for Correspondence

Lead author name
Nicolas Toussaint, Ph.D.
E: n.toussaint@ucl.ac.uk
1. **TABLE OF CONTENTS**

1. TABLE OF CONTENTS ............................................................................................................ 3  
2. INTRODUCTION ..................................................................................................................... 4  
3. IMAGING BIOMARKERS IN DEMENTIA ............................................................................. 4  
4. KEY IMAGING BIOMARKER PIPELINES ......................................................................... 5  
   4.1. PRE-PROCESSING OF STRUCTURAL T1 ................................................................. 6  
   4.2. GROUPWISE REGISTRATION .................................................................................... 8  
   4.3. BRAIN PARCELLATION ............................................................................................... 9  
   4.4. TISSUE SEGMENTATION ............................................................................................ 10  
   4.5. LONGITUDINAL CHANGE ......................................................................................... 12  
   4.6. AUTOMATED QUALITY CONTROL MEASURES ...................................................... 14  
5. REQUESTS FOR NEW PIPELINES: .................................................................................... 15  
6. DATA SHARING POLICY: ................................................................................................. 16  
7. REFERENCES ......................................................................................................................... 17  
8. APPENDIX: ADDITIONAL PIPELINES TO CONSIDER ............................................. 20
2. INTRODUCTION

Numerous observational studies on Alzheimer’s disease and other neurodegenerative disorders have accumulated large sets of imaging and phenomenological data that can be used to characterise the course of these diseases, even at the preclinical stages. These datasets are stored at various centres around the world, with a diverse amount of imaging, fluid, and cognitive data acquired. The resulting biomarkers extracted from the imaging data are highly dependent on the technique used and the software version of that technique. Finally, the computational requirements to store the original and derived images, as well as do all the processing, is a significant challenge. As a result, it is currently difficult to harness the statistical power that could be obtained by effectively combining these numerous cohorts together. One of the key aims of the VPH-DARE@IT project is to define data processing pipelines that extract imaging biomarkers from these cohorts for the purpose of mechanistic and phenomenological brain modelling, as well as for the proposed clinical decision support platform. This document describes a plan for implementing biomarkers into the VPH-DARE@IT infrastructure for use in analysing retrospective data cohorts as well as to provide tools for modellers in the prospective studies. First, we recommend key imaging biomarkers that serve as exemplar image processing workflows, or pipelines, implemented into VPH-SHARE infrastructure in order to meet Deliverable 3.3. These biomarkers are the most robust and thoroughly validated for dementia; thus, they will have the greatest utility for the VPH-DARE@IT community. As it will be inevitable that new needs will arise during the course of the project that will require new biomarkers to be developed, we have created a process for integrating new biomarker pipelines into the framework.

3. IMAGING BIOMARKERS IN DEMENTIA

The formal diagnosis of Alzheimer’s disease and many other dementias are currently based on clinical criteria ((Crutch et al., 2013; Gorno-Tempini et al., 2011; McKhann et al., 1984, 2001) that occur late in the disease process. The current understanding of the disease course, as shown by Figure 1 and in (Bateman et al., 2012; Jack et al., 2013; Villemagne et al., 2013), is that early misfolding of proteins are evident as much as 10 years before clinical onset. These changes are followed by signs of neuronal injury closer to clinical onset, and finally clinical manifestation of the disease as outlined by the above clinical criteria. Modern imaging methods can play a role in providing accurate quantitative measures that are surrogates for these changes. Amyloid PET imaging, either through the 11C-PiB compound or the numerous F18 tracers provide 3D images of amyloid plaque distribution. Surrogate markers of neuronal injury can be obtained using FDG-PET imaging to determine areas of hypometabolism in the brain that are consistent with the early stages of dementia (Minoshima, Frey, Koepppe, Foster, & Kuhl, 1995; Mosconi et al., 2006, 2008).

The most well-known and widely used biomarker is based on structural MRI to provide quantitative measures of macroscopic neurodegeneration represented as brain atrophy (Jack, 2011; Jack et al., 2010; Schott, Stevens, Rosser, & Fox, 2002). The dynamic change of structural MRI-based biomarkers is observed closest to clinical onset. These biomarkers are also highly correlated to disease progression as measured by clinical assessment. An important question when using these biomarkers is what region of the brain should be included in the measurement? Whole brain changes are robust but not very sensitive to changes within the small structures that are selectively affected by some neurodegenerative diseases (such as the hippocampi in Alzheimer’s disease). Expansion of the CSF within the lateral ventricles is quite a sensitive measure, as it can represent an amalgamation of small levels of diffuse atrophy throughout the brain. However, expansion of the lateral ventricles is typically observed in most forms of neurodegenerative dementias, thus it provides little specificity in terms of differential diagnosis. There are often smaller structures, such as the entorhinal cortex, hippocampus and precuneus in AD, where atrophy occurs at a considerably
higher rate than most areas of the brain, providing specificity, even at very early stages of the disease. The disadvantage to using one of these smaller regions is that the measurements have a higher variability, as they are more susceptible to partial volume and other imaging artefacts.

![Diagram of biomarker changes during Alzheimer’s disease]

**FIGURE 1:** PROPOSED ORDER OF BIOMARKER CHANGES DURING ALZHEIMER’S DISEASE. THE HORIZONTAL ACCESS REPRESENTS THE CLINICAL SEVERITY (LEFT BEING NORMAL, RIGHT BEING SEVERELY AFFECTED AND THE VERTICAL AXIS REPRESENTING THE DEGREE OF ABNORMALITY AS REPRESENTED BY THE BIOMARKER VALUE. (REPRINTED FROM JACK ET AL, LANCET NEUROLOGY, 12(2): 207-216, 2013)

4. **KEY IMAGING BIOMARKER PIPELINES**

For most of the work done as part of clinical decision support as well as the modelling in VPH-DARE, biomarkers involving structural MRI will be one of the most established and robust biomarkers to use. Structural MRI data is the most ubiquitous and standardised imaging modality in the retrospective studies. Thus, structural MRI based biomarkers will be the ones implemented as part of the completion of deliverable 3.3, so that the biomarkers can be extracted from the retrospective studies listed in deliverable 1.2. Biomarkers involving PET and advanced MRI sequences will be incorporated into pipelines in the future through the New Pipeline Implementation process outlined below. Some examples of these pipelines are listed below. It is important that all pipelines have a validation process to ensure that the pipeline is working correctly once implemented in the VPH-SHARE infrastructure and can be used effectively through the VPH-Dare Research Platform.

Some conventions are required for the efficient implementation of the pipelines. First, images will be stored using the Neuroimaging Informatics Technology Initiative (Nifti) data format (http://nifti.nimh.nih.gov/nifti-1/), unless the authors of a specific pipeline provide a
compelling reason that another format should be used. Since much of the imaging data will be
stored in DICOM image format, then converting these files into Nifti format should be the
first step during the pre-processing pipeline listed below. Surface formats will be stored in
one of the formats that are compatible with the GIMIAS software package
(http://www.gimias.org). Command line executables and scripts for the pipelines, along with
the required software dependencies should also be provided.

### 4.1. Pre-Processing of Structural T1

<table>
<thead>
<tr>
<th>Suitable data sets</th>
<th>All studies in VPH-DARE with structural T1 data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inputs</td>
<td>Raw structural T1 images (DICOM or Nifti), structural T2 and FLAIR images (optional)</td>
</tr>
<tr>
<td>Outputs</td>
<td>Pre-processed images, skull-stripped and bias corrected (Nifti format) along with a label image indicating the intracranial tissue</td>
</tr>
<tr>
<td>Software packages needed</td>
<td>dcm2nii, itkN4,</td>
</tr>
<tr>
<td>Expected Start Date</td>
<td>PM10</td>
</tr>
<tr>
<td>Expected Completion Date</td>
<td>PM14</td>
</tr>
</tbody>
</table>

Structural T1 images require a few pre-processing steps before extraction of clinically
relevant biomarkers can be performed. As mentioned above, DICOM images should first be
converted to the Nifti format. The two most common pre-processing steps are bias correction
and skull stripping. Bias correction (see, for example, Sled, Zijdenbos, & Evans, 1998)
removes intensity inhomogeneities caused by slight imperfections in the B0 magnetic field,
which cause low frequency spatial variations of intensity in the data. Skull stripping involves
removing most of the non-brain and extracranial tissue. It is important not to remove the
cerebrospinal fluid that bathes the brain, as identifying this component provides a good
estimation of total intracranial volume, which allows for covariation of head size, an
important nuisance covariate in most of these biomarkers (Barnes et al., 2010). In some cases,
geometric distortion correction of the images is also needed (Jovicich et al., 2006), as these
provide subtle warps that can sometimes have an effect on volume and atrophy calculations
depending on the MRI scanner and gradients used to acquire the data. These correction
methods typically require proprietary information about the scanner that may be difficult to
obtain, and thus this step should be avoided unless there are known issues with geometric
distortion within the study. An example of bias correction and skull stripping can be seen in
Figure 2.

Numerous methods are available for each of these steps. While most of these methods are
robust and provide sensible results there will be differences in the results that can have
follow-on effects to the biomarker extraction. Thus a standardised method that performs these
pre-processing steps would be ideal.

**Pipeline Process:**

1. Register (using 12 degrees of freedom) the image to a standard space atlas, such as
   MNI.
2. Obtain a rough brain mask by transferring the standard state brain mask back to the
   native image.
3. Run the bias correction algorithm on the image using ITK’s updated implementation
   of the N3 algorithm (known as N4).
4. Refine the brain mask by running a skull-stripping algorithm on the bias corrected
   image.
Validation Process:

1. A set of test data sets from the available studies, where these steps have already been performed outside the VPH-SHARE infrastructure and visually checked, should be used in the test version of the pipeline.
2. The resulting bias corrected image will be compared by examining the similarity in the bias corrected image and estimated bias field to the pre-computed version.
3. The skull stripping will be tested using the Dice overlap measure to determine the amount of agreement with the skull stripping pipeline and the pre-computed results.

FIGURE 2: (LEFT) NATIVE MRI IMAGE. IMAGE INHOMOGENEITIES CAN BE SEEN AS BRIGHT SPOTS ON THE ANTERIOR AND POSTERIOR REGIONS, (MIDDLE) BIAS CORRECTED VERSION OF THE SAME IMAGE, (RIGHT) YELLOW TRANSPARENCY INDICATES SKULL-STRIPPED REGION FOR USE WITH SUBSEQUENT BIOMARKERS.
4.2. Groupwise Registration

<table>
<thead>
<tr>
<th>Suitable data sets</th>
<th>All studies in VPH-DARE with structural T1 data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inputs</td>
<td>All pre-processed T1 images to include in registration (Nifti format)</td>
</tr>
<tr>
<td>Outputs</td>
<td>Deformation fields (Nifti format) to groupwise space, average groupwise image (Nifti format)</td>
</tr>
<tr>
<td>Software packages needed</td>
<td>NiftyReg</td>
</tr>
<tr>
<td>Expected Start Date</td>
<td>PM10</td>
</tr>
<tr>
<td>Expected Completion Date</td>
<td>PM14</td>
</tr>
</tbody>
</table>

Many algorithms require a consistent coordinate space to align the study images into, so that corresponding anatomical regions can be aligned and compared. There are many atlases available (MNI, ICBM, AAL) to the public; however, these atlases are often constructed on young individuals whose brains are not very similar morphologically to the elderly population that most of these studies consist of. The resulting registration between a brain and a dissimilar atlas is prone to more registration errors. An alternative method is to construct a groupwise average (Rohlfing, Brandt, Menzel, & Maurer, 2004) for this purpose, which consists of an iterative process of averaging the images together and then aligning all of the images to the average.

Pipeline Process:

1. Initialise the average. This could either be an atlas, a randomly chosen subject, or an average of the unaligned images.
2. Rigidly register all of the images to the average
3. Update the average with the most up to date version of the aligned images
4. Repeat using rigid registration in the early iterations and non-rigid registrations in the later iterations until the groupwise average converges.

Validation process:

1. Take a standard set of 100 images and perform groupwise registration using a number of other widely accepted registration techniques, such as DARTEL and Demons.
2. Compare the image similarity between the resulting atlas with the one provided by other registration methods.

![Flowchart](image)  
**FIGURE 3 FLOWCHART DESCRIBING THE GROUPWISE REGISTRATION PROCESS**
### 4.3. Brain Parcellation

<table>
<thead>
<tr>
<th>Suitable data sets</th>
<th>All studies in VPH-DARE with structural T1 data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inputs</td>
<td>Pre-processed T1 image, skull-stripped and bias corrected (Nifti format), template library</td>
</tr>
<tr>
<td>Outputs</td>
<td>Anatomically labelled image (Nifti format), volumes for each label</td>
</tr>
<tr>
<td>Software packages needed</td>
<td>NiftyReg, NiftySeg</td>
</tr>
<tr>
<td>Expected Start Date</td>
<td>PM12</td>
</tr>
<tr>
<td>Expected Completion Date</td>
<td>PM16</td>
</tr>
</tbody>
</table>

Brain parcellation consists of annotating each voxel of the brain with a label that represents an anatomic structure. By counting the number of voxels that contain the same label, volumetric measures for each structure can be obtained. At the heart of the parcellation pipeline is a technique known as multi-atlas segmentation propagation. This method uses a template library, or a collection of atlases, where a trained expert has already labelled the entire brain. Each of the templates, and the corresponding image containing the labels, is warped to the new image using a non-rigid registration. This results in all the atlases being registered to the new image, providing multiple candidate parcellations. These candidate parcellations are fused into a consensus parcellation using a label fusion process. There are many label fusion algorithms available; UCL uses an algorithm called STEPS that is locally weighted to anatomy that is similar on a voxel rather than global level. The atlases used for this parcellation framework come from the BrainColor segmentation datasets (http://www.braincolor.org/). Results from this algorithm are shown in Figure 4.

**Pipeline Process**

1. Register all template images to unseen image using first rigid, then non-rigid registration.
2. Transfer labels to new image using deformation fields resulting from registration process.
3. Fuse resulting labels together to form consensus label image.

**Validation Process**

1. Identify template library consisting of expertly drawn brain parcellations and perform brain parcellation in a leave-one out fashion, and compare the Dice overlap scores to the manually drawn regions.
Another important biomarker to extract from the structural T1 weighted images is the tissue composition of each voxel in terms of grey matter, white matter, and cerebrospinal fluid in the image. This provides benefits to the modellers in terms of being better able to describe the physical properties of the tissue for the mesh, as well as providing this information for multimodal processing, as PET, DWI and resting state fMRI do not have sufficient resolution or contrast to provide this information. Additional structural imaging sequences may be used, such as T2 and FLAIR that use different contrast weightings. They give complementary information to these algorithms and improve their accuracy, especially in deep grey matter nuclei and white matter.

The segmentation results in probabilistic maps (see Figure 5) representing the concentration of the tissue types at each voxel. When these probabilistic maps are spatially normalised so that anatomy is roughly aligned across subjects, then voxelwise statistical analysis can be performed in voxel-based morphometry methods.
Pipeline Process

1. GM, WM and CSF are typically estimated through a similar process as the brain parcellation atlas, using different labels and atlases.

Validation Process

1. The Brainweb MRI simulator provides a ground truth of GM, WM, and CSF image that can be degraded using noise and bias field. We will use this simulation at various levels of noise and bias to check the amount of agreement from the resulting segmentation.
4.5. **Longitudinal Change**

<table>
<thead>
<tr>
<th>Suitable data sets</th>
<th>All studies in VPH-DARE with structural T1 data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inputs</td>
<td>Two or more pre-processed T1 images, with mappings for each region to measure atrophy over</td>
</tr>
<tr>
<td>Outputs</td>
<td>Measures of brain loss between each image pair</td>
</tr>
<tr>
<td>Software packages needed</td>
<td>NiftyReg, NiftySeg</td>
</tr>
<tr>
<td>Expected Start Date</td>
<td>PM16</td>
</tr>
<tr>
<td>Expected Completion Date</td>
<td>PM20</td>
</tr>
</tbody>
</table>

While volumetric measures of structure of the whole brain and specific brain structures in serial scans can provide estimates of change over time, these are based on independent measures that are each susceptible to mistakes. Another approach is to perform a direct measurement of change, identifying the differences in intensity (Freeborough & Fox, 1997) or shape (Hua et al., 2013; Sehall et al., 2002) between the images and obtaining a quantitative measure of loss in volume from these differences. The conventional method has been pairwise, but there are now methods that perform multi-timepoint alignment and comparison of images that is consistent for the whole series of timepoints for a subject (Leung, Ridgway, Ourselin, & Fox, 2011; Reuter, Schmansky, Rosas, & Fischl, 2012).

**Pipeline Process**

1. Register the baseline and follow-up timepoints together. This is best done to a common space so that no bias is introduced.
2. If the registration is rigid/affine, perform the boundary shift integral on the exclusive OR region between the two regions, which will provide a volume estimation.
3. If the registration is non-rigid, compute the volume change by integrating the derivative of the Jacobi from the deformation field.

**Validation Process**

1. Compare the atrophy results between these direct methods and those using expert drawn regions. The results should be tightly correlated.
FIGURE 6 FLOWCHARTS FOR (TOP) VOXEL COMPRESSION MAPPING AND (BOTTOM) BOUNDARY SHIFT INTEGRAL
4.6. Automated Quality Control Measures

<table>
<thead>
<tr>
<th>Suitable data sets</th>
<th>All studies in VPH-DARE with structural T1 data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inputs</td>
<td>Results from biomarker extraction pipelines</td>
</tr>
<tr>
<td>Outputs</td>
<td>QC result (passed or action required), metrics on the resulting image</td>
</tr>
<tr>
<td>Software packages needed</td>
<td>NiftyReg, NiftySeg</td>
</tr>
<tr>
<td>Expected Start Date</td>
<td>PM12</td>
</tr>
<tr>
<td>Expected Completion Date</td>
<td>PM24</td>
</tr>
</tbody>
</table>

Ideal practice when extracting the above biomarkers is to visually review the results of the various steps to ensure that the processes ran successfully and produced a plausible result. However, given the size of the numerous cohorts and the number of biomarkers to extract, this approach is not plausible. As a result, pipelines will be needed to review the results to determine if they have been successful. These techniques could involve checking for volumes to be in normal range, reviewing metrics of similarity for an image when transformed into an atlas space, comparing volumetric differences with measures of change to see if there is a strong correlation.

Input: Interim and completed results from aforementioned pipelines

Output: Reports containing key image snapshots, graphs, and other metrics that describe the results of the data, along with an action needed or completed status for the pipeline.

Process:

1. Review registrations
2. Register derived images from pipeline into a standard space template, and compare overlap of regions with the standard space definition of these regions. The overlap would only require action if it were below a pre-specified Dice score for that region (i.e. larger regions should have higher Dice scores due to nature of measure).
3. Compare volumetric measurements of key biomarkers (GM, hippocampi, whole brain, TIV) with known values from pre-checked data using the pipeline and raise an action required if the values are great than 2 standard deviations away from a normal value expected for these results.

Validation process:

1. Compare a data set that contains both images suitable for analysis along with images that have known artefacts previously identified. Determine the success rate of the QC algorithms to pick the identified images.
5. REQUESTS FOR NEW PIPELINES:

During the course of the VPH-DARE@IT project, additional workflows will be required from a number of different partners:

- To process other modalities from the retrospective and prospective studies, such as fMRI or DWI
- To help better characterise the brain for the modelling applications by providing additional segmentation algorithms
- To provide the clinical decision platform with new biomarkers that have increased sensitivity and specificity
- To satisfy clinician’s or other researcher’s needs within the research platform.

Any collaborator within VPH-DARE@IT can request a new pipeline be deployed within the VPH-SHARE infrastructure to be accessible through the VPH-Dare@IT Research Platform. However, the process of successfully implementing and validating these pipelines within the VPH-SHARE infrastructure will take time and resources from the partners involved, and there may be times when prioritisation between two more pipelines will be required. Thus, we propose the following process for requesting an implementation of the pipeline.

1. The requestor will create a brief one page abstract describing the pipeline, similar to the format used for the examples above, which will include: the inputs required, the outputs produced and that will be stored back into the VPH-SHARE, the software packages needed for the pipeline, a list of the basic steps that comprise the pipeline, validation requirements to make sure that the pipeline has been successfully implemented, and any other specific computational requirements. A graphical representation of the pipeline is also suggested.

2. This abstract should then be submitted to the VPH-DARE@IT Pipeline Committee (VPC). This committee will consist of members who are clinicians, owners of the retrospective databases. Imaging biomarker developers, end-users of the research and clinical platform, and technical experts familiar with these platforms.

3. The VPC will review the application and determine what additional information is necessary. They will then review the pipeline to determine if this pipeline is unique or if a similar one is already available, that the method is sound scientifically, that the study data available is suitable for the requested pipeline, and how the priority for completing this pipeline compares with others currently under development.

4. The VPC will issue a decision on the pipeline of: (a) accepted: implementation of the pipeline should begin, (b) queued: the pipeline is put into the queue of other pipelines to be implemented, which will begin once resource is available, (c) queried: there is further information required about the pipeline before a final decision can be given, or (d) rejected: in its current form, the pipeline will not be implemented. The VPC will keep an online and updated registry of the status of the different pipelines.

5. Once the pipeline is implemented, the VPC will determine a key contact to work with the requestor on implementing the pipeline. The key contact will be someone either familiar with the methodology used in the pipeline or someone familiar with the VPH-SHARE infrastructure, depending on what is needed most. They will help further define the requirements with the requestor and create a testing and validation document that will serve as the document that will provide sufficient evidence that the pipeline has been successfully implemented within VPH-DARE@IT Research platform.

6. Implementation and testing will then be performed as per the document guideline. Once the pipeline produces the expected results, both groups will complete and sign the document, and the pipeline will be made available for to the greater community.

The initial abstract, testing and validation document, and any additional documentation for users on how to run the pipeline will be stored on the VPH-DARE@IT intranet (EMDesk) for all partners to access.
6. **Data Sharing Policy:**

VPH-DARE@IT has a specified database access policy that can be found in Deliverable 1.2. It should be possible to run any pipeline on imaging data for an available project given that the individual has access to this data before running the pipeline. The resulting biomarkers and images from these pipelines will be derived from these databases, and thus results from these pipelines should follow the same access policy as the original data themselves, unless otherwise agreed beforehand with the VPH-DARE@IT Study Board (VSB).
7. REFERENCES


8. APPENDIX: ADDITIONAL PIPELINES TO CONSIDER

CORTICAL THICKNESS MEASURES

<table>
<thead>
<tr>
<th>Suitable data sets</th>
<th>All studies in VPH-DARE with structural T1 data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inputs</td>
<td>Pre-processed T1 image, skull-stripped and bias corrected (Nifti format), T2/FLAIR images (optional)</td>
</tr>
<tr>
<td>Outputs</td>
<td>Surface representation of WM and GM, values of cortical thickness for given regions</td>
</tr>
<tr>
<td>Software packages needed</td>
<td>FreeSurfer</td>
</tr>
<tr>
<td>Expected Start Date</td>
<td></td>
</tr>
<tr>
<td>Expected Completion Date</td>
<td></td>
</tr>
</tbody>
</table>

In addition to specifically measuring the volume of specific structures, the thickness of the cortical GM ribbon has been shown also change size during atrophy (cites for FreeSurfer). These ribbons can then be registered to a spherical representation of the brain so that corresponding sulcal and gyral anatomy can be compared at a voxel wise analysis.

Pipeline Process: Consists of the multiple FreeSurfer steps. Please see their Wiki for a full description

Validation Pipeline: Using ADNI, which has publicly available results available for numerous versions, comparison to ensure same values are being achieved.