EUROPEAN COMMISSION
Directorate General for Communications Networks, Content and Technology

Sustainable and Secure Society
Health and Well-being

GRANT AGREEMENT

NUMBER — 689617 — EurValve

This **Agreement** ('the Agreement') is **between** the following parties:

on the one part,

*the **European Union** ('the EU'), represented by the European Commission ('the Commission')*[1],

represented for the purposes of signature of this Agreement by Head of Unit, Directorate General for Communications Networks, Content and Technology, Sustainable and Secure Society, Administration and Finance, Miguel GONZALEZ-SANCHO,

and

on the other part,

1. 'the coordinator':

THE UNIVERSITY OF SHEFFIELD (USFD), RC000667, established in FIRTH COURT WESTERN BANK, SHEFFIELD S10 2TN, United Kingdom, GB648238808, represented for the purposes of signing the Agreement by Deborah LODGE

and the following other beneficiaries, if they sign their 'Accession Form' (see Annex 3 and Article 56):

2. **ANSYS FRANCE SAS (ANSYS)** SAS, 389371816, established in PLACE GEORGES POMPIDOU 14-15, MONTIGNY LE BRETONNEUX 78180 , France, FR41389371816,

3. **Stichting Catharina Ziekenhuis (CATH)** NL6, 41087385, established in MICHELANGELOLAAN 2, EINDHOVEN 5623EJ, Netherlands, NL002655135B01,

4. **AKADEMIA GORNICZO-HUTNICZA IM. STANISLAWA STASZICA W KRAKOWIE (CYFRONET)**, 000001577, established in AL ADAMA MICKIEWICZA 30, KRAKOW 30-059, Poland, PL6750001923,

5. **DEUTSCHES HERZZENTRUM BERLIN (DHZB)** DE2, ., established in AUGUSTENBURGER PLATZ 1, BERLIN 13353, Germany, DE136623017,

6. **UNIVERSITE DE RENNES I (UR1)**, 193509361, established in RUE DU THABOR 2, RENNES CEDEX 35065, France, FR70193509361,

7. **MAX-DELBRUCK-CENTRUM FUR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT (MDC)**, established in ROBERT ROSSLE STRASSE 10, BERLIN 13125, Germany, DE811261930,

8. **PHILIPS ELECTRONICS NEDERLAND B.V. (PEN)** BV, 17008551, established in Boschdijk 525, EINDHOVEN 5621JG, Netherlands, NL001902106B01,

9. **Philips GmbH (PHILIPS)** AG, HRB74560, established in Luebeckertordamm 5, Hamburg 20099, Germany, DE812927597,

1 Text in *italics* shows the options of the Model Grant Agreement that are applicable to this Agreement.

10. **SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST (STH)**, established in BEECH HILL ROAD 8, SHEFFIELD S10 2SB, United Kingdom, GB654400165,

11. **THERENVA (THERENVA)** SAS, 500603287, established in 12 RUE PIERRE CORNEILLE, RENNES 35000, France, FR35500603287,

12. **TECHNISCHE UNIVERSITEIT EINDHOVEN (TU/e)**, 51278871, established in DEN DOLECH 2, EINDHOVEN 5612 AZ, Netherlands, NL001956218B01,

13. **UNIVERSITY OF BRISTOL (UBRIS)** GB22, RC000648, established in TYNDALL AVENUE SENATE HOUSE, BRISTOL BS8 1TH, United Kingdom, GB991261800,

Unless otherwise specified, references to ‘beneficiary’ or ‘beneficiaries’ include the coordinator.

The parties referred to above have agreed to enter into the Agreement under the terms and conditions below.

By signing the Agreement or the Accession Form, the beneficiaries accept the grant and agree to implement it under their own responsibility and in accordance with the Agreement, with all the obligations and conditions it sets out.

The Agreement is composed of:

Terms and Conditions

Annex 1 Description of the action

Annex 2 Estimated budget for the action

Annex 3 Accession Forms

Annex 4 Model for the financial statements

Annex 5 Model for the certificate on the financial statements

Annex 6 Model for the certificate on the methodology

TERMS AND CONDITIONS

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CHAPTER 1 GENERAL

ARTICLE 1 — SUBJECT OF THE AGREEMENT

This Agreement sets out the rights and obligations and the terms and conditions applicable to the grant awarded to the beneficiaries for implementing the action set out in Chapter 2.

CHAPTER 2 ACTION

ARTICLE 2 — ACTION TO BE IMPLEMENTED

The grant is awarded for the action entitled '***Personalised Decision Support for Heart Valve Disease — EurValve***' **('action')**, as described in Annex 1.

ARTICLE 3 — DURATION AND STARTING DATE OF THE ACTION

The duration of the action will be ***36*** **months** as of *1 February 2016* ('**starting date of the action**').

ARTICLE 4 — ESTIMATED BUDGET AND BUDGET TRANSFERS

4.1 Estimated budget

The '**estimated budget**' for the action is set out in Annex 2.

It contains the estimated eligible costs and the forms of costs, broken down by beneficiary and budget category (see Articles 5, 6).

4.2 Budget transfers

The estimated budget breakdown indicated in Annex 2 may be adjusted by transfers of amounts between beneficiaries or between budget categories (or both). This does not require an amendment according to Article 55, if the action is implemented as described in Annex 1.

However, the beneficiaries may not add costs relating to subcontracts not provided for in Annex 1, unless such additional subcontracts are approved by an amendment or in accordance with Article 13.

CHAPTER 3 GRANT

ARTICLE 5 — GRANT AMOUNT, FORM OF GRANT, REIMBURSEMENT RATES AND FORMS OF COSTS

5.1 Maximum grant amount

The '**maximum grant amount**' is **EUR 4,998,012.50** (four million nine hundred and ninety eight thousand twelve EURO and fifty eurocents).

5.2 Form of grant, reimbursement rates and forms of costs

The grant reimburses ***100% of the action's eligible costs*** (see Article 6) ('**reimbursement of eligible costs grant**') (see Annex 2).

The estimated eligible costs of the action are EUR **4,998,012.51** (four million nine hundred and ninety eight thousand twelve EURO and fifty one eurocents).

Eligible costs (see Article 6) must be declared under the following forms ('**forms of costs**'):

(a) for **direct personnel costs**:

- as actually incurred costs ('**actual costs**') or
- on the basis of an amount per unit calculated by the beneficiary in accordance with its usual cost accounting practices ('**unit costs**').

Personnel **costs for SME owners** or **beneficiaries that are natural persons** not receiving a salary (see Article 6.2, Points A.4 and A.5) must be declared on the basis of the amount per unit set out in Annex 2 (**unit costs**);

(b) for **direct costs for subcontracting**: as actually incurred costs (**actual costs**);

(c) for **direct costs of providing financial support to third parties**: *not applicable;*

(d) for **other direct costs**: as actually incurred costs (**actual costs**);

(e) for **indirect costs**: on the basis of a flat-rate applied as set out in Article 6.2, Point E ('**flat-rate costs**');

(f) ***specific cost category(ies):*** *not applicable.*

5.3 Final grant amount — Calculation

The '**final grant amount**' depends on the actual extent to which the action is implemented in accordance with the Agreement's terms and conditions.

This amount is calculated by the *Commission* — when the payment of the balance is made (see Article 21.4) — in the following steps:

Step 1 – Application of the reimbursement rates to the eligible costs

Step 2 – Limit to the maximum grant amount

Step 3 – Reduction due to the no-profit rule

Step 4 – Reduction due to improper implementation or breach of other obligations

5.3.1 Step 1 — Application of the reimbursement rates to the eligible costs

The reimbursement rate(s) (see Article 5.2) are applied to the eligible costs (actual costs, unit costs and flat-rate costs; see Article 6) declared by the beneficiaries (see Article 20) and approved by the *Commission* (see Article 21).

5.3.2 Step 2 — Limit to the maximum grant amount

If the amount obtained following Step 1 is higher than the maximum grant amount set out in Article 5.1, it will be limited to the latter.

5.3.3 Step 3 — Reduction due to the no-profit rule

The grant must not produce a profit.

'**Profit**' means the surplus of the amount obtained following Steps 1 and 2 plus the action's total receipts, over the action's total eligible costs.

The '**action's total eligible costs**' are the consolidated total eligible costs approved by the *Commission*.

The '**action's total receipts**' are the consolidated total receipts generated during its duration (see Article 3).

The following are considered **receipts**:

(a) income generated by the action; if the income is generated from selling equipment or other assets purchased under the Agreement, the receipt is up to the amount declared as eligible under the Agreement;

(b) financial contributions given by third parties to the beneficiary specifically to be used for the action, and

(c) in-kind contributions provided by third parties free of charge and specifically to be used for the action, if they have been declared as eligible costs.

The following are however not considered receipts:

(a) income generated by exploiting the action's results (see Article 28);

(b) financial contributions by third parties, if they may be used to cover costs other than the eligible costs (see Article 6);

(c) financial contributions by third parties with no obligation to repay any amount unused at the end of the period set out in Article 3.

If there is a profit, it will be deducted from the amount obtained following Steps 1 and 2.

5.3.4 Step 4 — Reduction due to improper implementation or breach of other obligations — Reduced grant amount — Calculation

If the grant is reduced (see Article 43), the *Commission* will calculate the reduced grant amount by deducting the amount of the reduction (calculated in proportion to the improper implementation of the action or to the seriousness of the breach of obligations in accordance with Article 43.2) from the maximum grant amount set out in Article 5.1.

The final grant amount will be the lower of the following two:

- the amount obtained following Steps 1 to 3 or

- the reduced grant amount following Step 4.

5.4 Revised final grant amount — Calculation

If — after the payment of the balance (in particular, after checks, reviews, audits or investigations; see Article 22) — the *Commission* rejects costs (see Article 42) or reduces the grant (see Article 43), it will calculate the '**revised final grant amount**' for the beneficiary concerned by the findings.

This amount is calculated by the *Commission* on the basis of the findings, as follows:

- in case of **rejection of costs**: by applying the reimbursement rate to the revised eligible costs approved by the *Commission* for the beneficiary concerned;

- in case of **reduction of the grant**: by calculating the concerned beneficiary's share in the grant amount reduced in proportion to its improper implementation of the action or to the seriousness of its breach of obligations (see Article 43.2).

In case of **rejection of costs and reduction of the grant**, the revised final grant amount for the beneficiary concerned will be the lower of the two amounts above.

ARTICLE 6 — ELIGIBLE AND INELIGIBLE COSTS

6.1 General conditions for costs to be eligible

'**Eligible costs**' are costs that meet the following criteria:

(a) for **actual costs**:

(i) they must be actually incurred by the beneficiary;

(ii) they must be incurred in the period set out in Article 3, with the exception of costs relating to the submission of the periodic report for the last reporting period and the final report (see Article 20);

(iii) they must be indicated in the estimated budget set out in Annex 2;

(iv) they must be incurred in connection with the action as described in Annex 1 and necessary for its implementation;

(v) they must be identifiable and verifiable, in particular recorded in the beneficiary's accounts in accordance with the accounting standards applicable in the country where the beneficiary is established and with the beneficiary's usual cost accounting practices;

(vi) they must comply with the applicable national law on taxes, labour and social security, and

(vii) they must be reasonable, justified and must comply with the principle of sound financial management, in particular regarding economy and efficiency;

(b) for **unit costs**:

(i) they must be calculated as follows:

{amounts per unit set out in Annex 2 or calculated by the beneficiary in accordance with its usual cost accounting practices (see Article 6.2, Point A)

multiplied by

the number of actual units};

(ii) the number of actual units must comply with the following conditions:

- the units must be actually used or produced in the period set out in Article 3;
- the units must be necessary for implementing the action or produced by it, and
- the number of units must be identifiable and verifiable, in particular supported by records and documentation (see Article 18);

(c) for **flat-rate costs**:

(i) they must be calculated by applying the flat-rate set out in Annex 2, and

(ii) the costs (actual costs or unit costs) to which the flat-rate is applied must comply with the conditions for eligibility set out in this Article.

6.2 Specific conditions for costs to be eligible

Costs are eligible if they comply with the general conditions (see above) and the specific conditions set out below for each of the following budget categories:

A. direct personnel costs;
B. direct costs of subcontracting;
C. *not applicable;*
D. other direct costs;
E. indirect costs;
F. *not applicable.*

'Direct costs' are costs that are directly linked to the action implementation and can therefore be attributed to it directly. They must not include any indirect costs (see Point E below).

'Indirect costs' are costs that are not directly linked to the action implementation and therefore cannot be attributed directly to it.

A. Direct personnel costs

Types of eligible personnel costs

A.1 **Personnel costs** are eligible, if they are related to personnel working for the beneficiary under an employment contract (or equivalent appointing act) and assigned to the action ('**costs for employees (or equivalent)**'). They must be limited to salaries (including during parental leave), social security contributions, taxes and other costs included in the **remuneration**, if they arise from national law or the employment contract (or equivalent appointing act).

Beneficiaries that are non-profit legal entities[2] may also declare as personnel costs **additional remuneration** for personnel assigned to the action (including payments on the basis of supplementary contracts regardless of their nature), if:

(a) it is part of the beneficiary's usual remuneration practices and is paid in a consistent manner whenever the same kind of work or expertise is required;

(b) the criteria used to calculate the supplementary payments are objective and generally applied by the beneficiary, regardless of the source of funding used.

Additional remuneration for personnel assigned to the action is eligible up to the following amount:

(a) if the person works full time and exclusively on the action during the full year: up to EUR 8 000;

(b) if the person works exclusively on the action but not full-time or not for the full year: up to the corresponding pro-rata amount of EUR 8 000, or

(c) if the person does not work exclusively on the action: up to a pro-rata amount calculated as follows:

{{EUR 8 000

divided by

the number of annual productive hours (see below)},

multiplied by

the number of hours that the person has worked on the action during the year}.

A.2 The **costs for natural persons working under a direct contract** with the beneficiary other than an employment contract are eligible personnel costs, if:

(a) the person works under the beneficiary's instructions and, unless otherwise agreed with the beneficiary, on the beneficiary's premises;

(b) the result of the work carried out belongs to the beneficiary, and

(c) the costs are not significantly different from those for personnel performing similar tasks under an employment contract with the beneficiary.

A.3 The **costs of personnel seconded by a third party against payment** are eligible personnel costs, if the conditions in Article 11.1 are met.

[2] For the definition, see Article 2.1(14) of the Rules for Participation Regulation No 1290/2013: '**non-profit legal entity**' means a legal entity which by its legal form is non-profit-making or which has a legal or statutory obligation not to distribute profits to its shareholders or individual members.

A.4 **Costs of owners** of beneficiaries that are small and medium-sized enterprises ('**SME owners**') who are working on the action and who do not receive a salary are eligible personnel costs, if they correspond to the amount per unit set out in Annex 2 multiplied by the number of actual hours worked on the action.

A.5 **Costs of 'beneficiaries that are natural persons'** not receiving a salary are eligible personnel costs, if they correspond to the amount per unit set out in Annex 2 multiplied by the number of actual hours worked on the action.

Calculation

Personnel costs must be calculated by the beneficiaries as follows:

{{hourly rate

multiplied by

the number of actual hours worked on the action},

plus

for non-profit legal entities: additional remuneration to personnel assigned to the action under the conditions set out above (Point A.1)}.

The number of actual hours declared for a person must be identifiable and verifiable (see Article 18).

The total number of hours declared in EU or Euratom grants, for a person for a year, cannot be higher than the annual productive hours used for the calculations of the hourly rate. Therefore, the maximum number of hours that can be declared for the grant is:

{the number of annual productive hours for the year (see below)

minus

total number of hours declared by the beneficiary for that person in that year for other EU or Euratom grants}.

The '**hourly rate**' is one of the following:

(a) for personnel costs declared as **actual costs:** the hourly rate is the amount calculated as follows:

{actual annual personnel costs (excluding additional remuneration) for the person

divided by

number of annual productive hours}.

The beneficiaries must use the annual personnel costs and the number of annual productive hours for each financial year covered by the reporting period. If a financial year is not closed at the end of the reporting period, the beneficiaries must use the hourly rate of the last closed financial year available.

For the 'number of annual productive hours', the beneficiaries may choose one of the following:

(i) 'fixed number of hours': 1 720 hours for persons working full time (or corresponding pro-rata for persons not working full time);

(ii) 'individual annual productive hours': the total number of hours worked by the person in the year for the beneficiary, calculated as follows:

{annual workable hours of the person (according to the employment contract, applicable collective labour agreement or national law)

plus

overtime worked

minus

absences (such as sick leave and special leave)}.

'Annual workable hours' means the period during which the personnel must be working, at the employer's disposal and carrying out his/her activity or duties under the employment contract, applicable collective labour agreement or national working time legislation.

If the contract (or applicable collective labour agreement or national working time legislation) does not allow to determine the annual workable hours, this option cannot be used;

(iii) 'standard annual productive hours': the 'standard number of annual hours' generally applied by the beneficiary for its personnel in accordance with its usual cost accounting practices. This number must be at least 90% of the 'standard annual workable hours'.

If there is no applicable reference for the standard annual workable hours, this option cannot be used.

For all options, the actual time spent on **parental leave** by a person assigned to the action may be deducted from the number of annual productive hours;

(b) for personnel costs declared on the basis of **unit costs**: the hourly rate is one of the following:

(i) for SME owners or beneficiaries that are natural persons: the hourly rate set out in Annex 2 (see Points A.4 and A.5 above), or

(ii) for personnel costs declared on the basis of the beneficiary's usual cost accounting practices: the hourly rate calculated by the beneficiary in accordance with its usual cost accounting practices, if:

- the cost accounting practices used are applied in a consistent manner, based on objective criteria, regardless of the source of funding;

- the hourly rate is calculated using the actual personnel costs recorded in the beneficiary's accounts, excluding any ineligible cost or costs included in other budget categories.

The actual personnel costs may be adjusted by the beneficiary on the basis of budgeted or estimated elements. Those elements must be relevant for calculating

the personnel costs, reasonable and correspond to objective and verifiable information;

and

- the hourly rate is calculated using the number of annual productive hours (see above).

B. Direct costs of subcontracting (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are eligible if the conditions in Article 13.1.1 are met.

C. Direct costs of providing financial support to third parties *not applicable.*

D. Other direct costs

D.1 **Travel costs and related subsistence allowances** (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are eligible if they are in line with the beneficiary's usual practices on travel.

D.2 *The **depreciation costs of equipment, infrastructure or other assets** (new or second-hand) as recorded in the beneficiary's accounts are eligible, if they were purchased in accordance with Article 10.1.1 and written off in accordance with international accounting standards and the beneficiary's usual accounting practices.*

*The **costs of renting or leasing** equipment, infrastructure or other assets (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are also eligible, if they do not exceed the depreciation costs of similar equipment, infrastructure or assets and do not include any financing fees.*

*The costs of equipment, infrastructure or other assets **contributed in-kind against payment** are eligible, if they do not exceed the depreciation costs of similar equipment, infrastructure or assets, do not include any financing fees and if the conditions in Article 11.1 are met.*

The only portion of the costs that will be taken into account is that which corresponds to the duration of the action and rate of actual use for the purposes of the action.

D.3 **Costs of other goods and services** (including related duties, taxes and charges such as non-deductible value added tax (VAT) paid by the beneficiary) are eligible, if they are:

(a) purchased specifically for the action and in accordance with Article 10.1.1 or

(b) contributed in kind against payment and in accordance with Article 11.1.

Such goods and services include, for instance, consumables and supplies, dissemination (including open access), protection of results, certificates on the financial statements (if they are required by the Agreement), certificates on the methodology, translations and publications.

D.4 **Capitalised and operating costs of 'large research infrastructure'**[3] *directly used for the action are eligible, if:*

(a) the value of the large research infrastructure represents at least 75% of the total fixed assets (at historical value in its last closed balance sheet before the date of the signature of the Agreement or as determined on the basis of the rental and leasing costs of the research infrastructure[4]*);*

*(b) the beneficiary's methodology for declaring the costs for large research infrastructure has been positively assessed by the Commission ('**ex-ante assessment**');*

(c) the beneficiary declares as direct eligible costs only the portion which corresponds to the duration of the action and the rate of actual use for the purposes of the action, and

(d) they comply with the conditions as further detailed in the annotations to the H2020 grant agreements.

E. Indirect costs

Indirect costs are eligible if they are declared on the basis of the flat-rate of 25% of the eligible direct costs (see Article 5.2 and Points A to D above), from which are excluded:

(a) costs of subcontracting and

(b) costs of in-kind contributions provided by third parties which are not used on the beneficiary's premises;

(c) *not applicable;*

(d) *not applicable.*

Beneficiaries receiving an operating grant[5] financed by the EU or Euratom budget cannot declare indirect costs for the period covered by the operating grant.

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[3] '**Large research infrastructure**' means research infrastructure of a total value of at least EUR 20 million, for a beneficiary, calculated as the sum of historical asset values of each individual research infrastructure of that beneficiary, as they appear in its last closed balance sheet before the date of the signature of the Agreement or as determined on the basis of the rental and leasing costs of the research infrastructure.

[4] For the definition, see Article 2(6) of Regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020) (OJ L 347, 20.12.2013 p.104)-('**Horizon 2020 Framework Programme Regulation No 1291/2013**'): '**Research infrastructure**' are facilities, resources and services that are used by the research communities to conduct research and foster innovation in their fields. Where relevant, they may be used beyond research, e.g. for education or public services. They include: major scientific equipment (or sets of instruments); knowledge-based resources such as collections, archives or scientific data; e-infrastructures such as data and computing systems and communication networks; and any other infrastructure of a unique nature essential to achieve excellence in research and innovation. Such infrastructures may be 'single-sited', 'virtual' or 'distributed'.

[5] For the definition, see Article 121(1)(b) of Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council of 25 October 2012 on the financial rules applicable to the general budget of the Union and repealing Council Regulation (EC, Euratom) No 1605/2002 (OJ L 218, 26.10.2012, p.1) ('**Financial Regulation No 966/2012**'): '**operating grant**' means direct financial contribution, by way of donation, from the budget in order to finance the functioning of a body which pursues an aim of general EU interest or has an objective forming part of and supporting an EU policy.

F. *Specific cost category(ies)*

Not applicable

6.3 Conditions for costs of linked third parties to be eligible

not applicable

6.4 Conditions for in-kind contributions provided by third parties free of charge to be eligible

In-kind contributions provided free of charge are eligible direct costs (for the beneficiary), if the costs incurred by the third party fulfil — *mutatis mutandis* — the general and specific conditions for eligibility set out in this Article (Article 6.1 and 6.2) and Article 12.1.

6.5 Ineligible costs

'**Ineligible costs**' are:

(a) costs that do not comply with the conditions set out above (Article 6.1 to 6.4), in particular:

(i) costs related to return on capital;

(ii) debt and debt service charges;

(iii) provisions for future losses or debts;

(iv) interest owed;

(v) doubtful debts;

(vi) currency exchange losses;

(vii) bank costs charged by the beneficiary's bank for transfers from the *Commission*;

(viii) excessive or reckless expenditure;

(ix) deductible VAT;

(x) costs incurred during suspension of the implementation of the action (see Article 49);

(b) costs declared under another EU or Euratom grant (including grants awarded by a Member State and financed by the EU or Euratom budget and grants awarded by bodies other than the *Commission* for the purpose of implementing the EU or Euratom budget); in particular, indirect costs if the beneficiary is already receiving an operating grant financed by the EU or Euratom budget in the same period.

6.6 Consequences of declaration of ineligible costs

Declared costs that are ineligible will be rejected (see Article 42).

This may also lead to any of the other measures described in Chapter 6.

CHAPTER 4 RIGHTS AND OBLIGATIONS OF THE PARTIES

SECTION 1 RIGHTS AND OBLIGATIONS RELATED TO IMPLEMENTING THE ACTION

ARTICLE 7 — GENERAL OBLIGATION TO PROPERLY IMPLEMENT THE ACTION

7.1 General obligation to properly implement the action

The beneficiaries must implement the action as described in Annex 1 and in compliance with the provisions of the Agreement and all legal obligations under applicable EU, international and national law.

7.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 8 — RESOURCES TO IMPLEMENT THE ACTION — THIRD PARTIES INVOLVED IN THE ACTION

The beneficiaries must have the appropriate resources to implement the action.

If it is necessary to implement the action, the beneficiaries may:

- purchase goods, works and services (see Article 10);
- use in-kind contributions provided by third parties against payment (see Article 11);
- use in-kind contributions provided by third parties free of charge (see Article 12);
- call upon subcontractors to implement action tasks described in Annex 1 (see Article 13);
- call upon linked third parties to implement action tasks described in Annex 1 (see Article 14).

In these cases, the beneficiaries retain sole responsibility towards the *Commission* and the other beneficiaries for implementing the action.

ARTICLE 9 — IMPLEMENTATION OF ACTION TASKS BY BENEFICIARIES NOT RECEIVING EU FUNDING

Not applicable

ARTICLE 10 — PURCHASE OF GOODS, WORKS OR SERVICES

10.1 Rules for purchasing goods, works or services

10.1.1 If necessary to implement the action, the beneficiaries may purchase goods, works or services.

The beneficiaries must make such purchases ensuring the best value for money or, if appropriate, the lowest price. In doing so, they must avoid any conflict of interests (see Article 35).

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards their contractors.

10.1.2 Beneficiaries that are 'contracting authorities' within the meaning of Directive 2004/18/EC[6] or 'contracting entities' within the meaning of Directive 2004/17/EC[7] must comply with the applicable national law on public procurement.

10.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under Article 10.1.1, the costs related to the contract concerned will be ineligible (see Article 6) and will be rejected (see Article 42).

If a beneficiary breaches any of its obligations under Article 10.1.2, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 11 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES AGAINST PAYMENT

11.1 Rules for the use of in-kind contributions against payment

If necessary to implement the action, the beneficiaries may use in-kind contributions provided by third parties against payment.

The beneficiaries may declare costs related to the payment of in-kind contributions as eligible (see Article 6.1 and 6.2), up to the third parties' costs for the seconded persons, contributed equipment, infrastructure or other assets or other contributed goods and services.

The third parties and their contributions must be set out in Annex 1. The *Commission* may however approve in-kind contributions not set out in Annex 1 without amendment (see Article 55), if:

- they are specifically justified in the periodic technical report and

- their use does not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards the third parties.

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[6] Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public work contracts, public supply contracts and public service contracts (OJ L 134, 30.04.2004, p. 114).

[7] Directive 2004/17/EC of the European Parliament and of the Council of 31 March 2004 coordinating the procurement procedures of entities operating in the water, energy, transport and postal services sectors (OJ L 134, 30.04.2004, p. 1).

11.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the costs related to the payment of the in-kind contribution will be ineligible (see Article 6) and will be rejected (see Article 42).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 12 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES FREE OF CHARGE

12.1 Rules for the use of in-kind contributions free of charge

If necessary to implement the action, the beneficiaries may use in-kind contributions provided by third parties free of charge.

The beneficiaries may declare costs incurred by the third parties for the seconded persons, contributed equipment, infrastructure or other assets or other contributed goods and services as eligible in accordance with Article 6.4.

The third parties and their contributions must be set out in Annex 1. The *Commission* may however approve in-kind contributions not set out in Annex 1 without amendment (see Article 55), if:

- they are specifically justified in the periodic technical report and
- their use does not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards the third parties.

12.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the costs incurred by the third parties related to the in-kind contribution will be ineligible (see Article 6) and will be rejected (see Article 42).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 13 — IMPLEMENTATION OF ACTION TASKS BY SUBCONTRACTORS

13.1 Rules for subcontracting action tasks

13.1.1 If necessary to implement the action, the beneficiaries may award subcontracts covering the implementation of certain action tasks described in Annex 1.

Subcontracting may cover only a limited part of the action.

The beneficiaries must award the subcontracts ensuring the best value for money or, if appropriate, the lowest price. In doing so, they must avoid any conflict of interests (see Article 35).

The tasks to be implemented and the estimated cost for each subcontract must be set out in Annex 1 and the total estimated costs of subcontracting per beneficiary must be set out in Annex 2. The

Commission may however approve subcontracts not set out in Annex 1 and 2 without amendment (see Article 55), if:

- they are specifically justified in the periodic technical report and

- they do not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

The beneficiaries must ensure that the Commission, the European Court of Auditors (ECA) and the European Anti-Fraud Office (OLAF) can exercise their rights under Articles 22 and 23 also towards their subcontractors.

13.1.2 The beneficiaries must ensure that their obligations under Articles 35, 36, 38 and 46 also apply to the subcontractors.

Beneficiaries that are 'contracting authorities' within the meaning of Directive 2004/18/EC or 'contracting entities' within the meaning of Directive 2004/17/EC must comply with the applicable national law on public procurement.

13.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under Article 13.1.1, the costs related to the subcontract concerned will be ineligible (see Article 6) and will be rejected (see Article 42).

If a beneficiary breaches any of its obligations under Article 13.1.2, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 14 — IMPLEMENTATION OF ACTION TASKS BY LINKED THIRD PARTIES

Not applicable

ARTICLE 15 — FINANCIAL SUPPORT TO THIRD PARTIES

15.1 Rules for providing financial support to third parties

Not applicable

15.2 Financial support in the form of prizes

Not applicable

15.3 Consequences of non-compliance

Not applicable

ARTICLE 16 — PROVISION OF TRANS-NATIONAL OR VIRTUAL ACCESS TO RESEARCH INFRASTRUCTURE

16.1 Rules for providing trans-national access to research infrastructure

Not applicable

16.2 Rules for providing virtual access to research infrastructure

Not applicable

16.3 Consequences of non-compliance

Not applicable

SECTION 2 RIGHTS AND OBLIGATIONS RELATED TO THE GRANT ADMINISTRATION

ARTICLE 17 — GENERAL OBLIGATION TO INFORM

17.1 General obligation to provide information upon request

The beneficiaries must provide — during implementation of the action or afterwards and in accordance with Article 41.2 — any information requested in order to verify eligibility of the costs, proper implementation of the action and compliance with any other obligation under the Agreement.

17.2 Obligation to keep information up to date and to inform about events and circumstances likely to affect the Agreement

Each beneficiary must keep information stored in the 'Beneficiary Register' (via the electronic exchange system; see Article 52) up to date, in particular, its name, address, legal representatives, legal form and organisation type.

Each beneficiary must immediately inform the coordinator — which must immediately inform the *Commission* and the other beneficiaries — of any of the following:

(a) **events** which are likely to affect significantly or delay the implementation of the action or the EU's financial interests, in particular:

  (i) changes in its legal, financial, technical, organisational or ownership situation

(b) **circumstances** affecting:

  (i) the decision to award the grant or

  (ii) compliance with requirements under the Agreement.

17.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 18 — KEEPING RECORDS — SUPPORTING DOCUMENTATION

18.1 Obligation to keep records and other supporting documentation

The beneficiaries must — for a period of *five* years after the payment of the balance — keep records and other supporting documentation in order to prove the proper implementation of the action and the costs they declare as eligible.

They must make them available upon request (see Article 17) or in the context of checks, reviews, audits or investigations (see Article 22).

If there are on-going checks, reviews, audits, investigations, litigation or other pursuits of claims under the Agreement (including the extension of findings; see Articles 22), the beneficiaries must keep the records and other supporting documentation until the end of these procedures.

The beneficiaries must keep the original documents. Digital and digitalised documents are considered originals if they are authorised by the applicable national law. The *Commission* may accept non-original documents if it considers that they offer a comparable level of assurance.

18.1.1 Records and other supporting documentation on the scientific and technical implementation

The beneficiaries must keep records and other supporting documentation on scientific and technical implementation of the action in line with the accepted standards in the respective field.

18.1.2 Records and other documentation to support the costs declared

The beneficiaries must keep the records and documentation supporting the costs declared, in particular the following:

(a) for **actual costs**: adequate records and other supporting documentation to prove the costs declared, such as contracts, subcontracts, invoices and accounting records. In addition, the beneficiaries' usual cost accounting practices and internal control procedures must enable direct reconciliation between the amounts declared, the amounts recorded in their accounts and the amounts stated in the supporting documentation;

(b) for **unit costs**: adequate records and other supporting documentation to prove the number of units declared. Beneficiaries do not need to identify the actual eligible costs covered or to keep or provide supporting documentation (such as accounting statements) to prove the amount per unit.

In addition, **for direct personnel costs declared as unit costs calculated in accordance with the beneficiary's usual cost accounting practices**, the beneficiaries must keep adequate

records and documentation to prove that the cost accounting practices used comply with the conditions set out in Article 6.2, Point A.

The beneficiaries may submit to the Commission, for approval, a certificate (drawn up in accordance with Annex 6) stating that their usual cost accounting practices comply with these conditions ('**certificate on the methodology**'). If the certificate is approved, costs declared in line with this methodology will not be challenged subsequently, unless the beneficiaries have concealed information for the purpose of the approval.

(c) for **flat-rate costs**: adequate records and other supporting documentation to prove the eligibility of the costs to which the flat-rate is applied. The beneficiaries do not need to identify the costs covered or provide supporting documentation (such as accounting statements) to prove the amount declared at a flat-rate.

In addition, for **personnel costs** (declared as actual costs or on the basis of unit costs), the beneficiaries must keep **time records** for the number of hours declared. The time records must be in writing and approved by the persons working on the action and their supervisors, at least monthly. In the absence of reliable time records of the hours worked on the action, the *Commission* may accept alternative evidence supporting the number of hours declared, if it considers that it offers an adequate level of assurance.

As an exception, for **persons working exclusively on the action**, there is no need to keep time records, if the beneficiary signs a **declaration** confirming that the persons concerned have worked exclusively on the action.

18.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, costs insufficiently substantiated will be ineligible (see Article 6) and will be rejected (see Article 42), and the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 19 — SUBMISSION OF DELIVERABLES

19.1 Obligation to submit deliverables

The coordinator must submit the '**deliverables**' identified in Annex 1, in accordance with the timing and conditions set out in it.

19.2 Consequences of non-compliance

If the coordinator breaches any of its obligations under this Article, the *Commission* may apply any of the measures described in Chapter 6.

ARTICLE 20 — REPORTING — PAYMENT REQUESTS

20.1 Obligation to submit reports

The coordinator must submit to the *Commission* (see Article 52) the technical and financial reports set out in this Article. These reports include the requests for payment and must be drawn up using the forms and templates provided in the electronic exchange system (see Article 52).

20.2 Reporting periods

The action is divided into the following '**reporting periods**':

- RP1: from month 1 to month 18
- *RP2: from month 19 to month 36*

20.3 Periodic reports — Requests for interim payments

The coordinator must submit a periodic report within 60 days following the end of each reporting period.

The **periodic report** must include the following:

(a) a '**periodic technical report**' containing:

(i) an **explanation of the work carried out** by the beneficiaries;

(ii) an **overview of the progress** towards the objectives of the action, including milestones and deliverables identified in Annex 1.

This report must include explanations justifying the differences between work expected to be carried out in accordance with Annex 1 and that actually carried out.

The report must also detail the exploitation and dissemination of the results and — if required in Annex 1 — an updated '**plan for the exploitation and dissemination of the results**';

(iii) a **summary** for publication by the *Commission*;

(iv) the answers to the '**questionnaire**', covering issues related to the action implementation and the economic and societal impact, notably in the context of the Horizon 2020 key performance indicators and the Horizon 2020 monitoring requirements;

(b) a '**periodic financial report**' containing:

(i) an '**individual financial statement**' (see Annex 4) from each beneficiary, for the reporting period concerned.

The individual financial statement must detail the eligible costs (actual costs, unit costs and flat-rate costs; see Article 6) for each budget category (see Annex 2).

The beneficiaries must declare all eligible costs, even if — for actual costs, unit costs and flat-rate costs — they exceed the amounts indicated in the estimated budget (see Annex

2). Amounts which are not declared in the individual financial statement will not be taken into account by the *Commission*.

If an individual financial statement is not submitted for a reporting period, it may be included in the periodic financial report for the next reporting period.

The individual financial statements of the last reporting period must also detail the **receipts of the action** (see Article 5.3.3).

Each beneficiary must **certify** that:

- the information provided is full, reliable and true;
- the costs declared are eligible (see Article 6);
- the costs can be substantiated by adequate records and supporting documentation (see Article 18) that will be produced upon request (see Article 17) or in the context of checks, reviews, audits and investigations (see Article 22), and
- for the last reporting period: that all the receipts have been declared (see Article 5.3.3);

(ii) an **explanation of the use of resources** and the information on subcontracting (see Article 13) and in-kind contributions provided by third parties (see Articles 11 and 12) from each beneficiary, for the reporting period concerned;

(iii) *not applicable;*

(iv) a '**periodic summary financial statement**' (see Annex 4), created automatically by the electronic exchange system, consolidating the individual financial statements for the reporting period concerned and including — except for the last reporting period — the **request for interim payment**.

20.4 Final report — Request for payment of the balance

In addition to the periodic report for the last reporting period, the coordinator must submit the final report within 60 days following the end of the last reporting period.

The **final report** must include the following:

(a) a '**final technical report**' with a **summary** for publication containing:

(i) an overview of the results and their exploitation and dissemination;

(ii) the conclusions on the action, and

(iii) the socio-economic impact of the action;

(b) a '**final financial report**' containing:

(i) a '**final summary financial statement**' (see Annex 4), created automatically by the electronic exchange system, consolidating the individual financial statements for all reporting periods and including the **request for payment of the balance** and

(ii) a '**certificate on the financial statements**' (drawn up in accordance with Annex 5) for each beneficiary , if it requests a total contribution of EUR 325 000 or more, as reimbursement of actual costs and unit costs calculated on the basis of its usual cost accounting practices (see Article 5.2 and Article 6.2, Point A).

20.5 Information on cumulative expenditure incurred

Not applicable

20.6 Currency for financial statements and conversion into euro

Financial statements must be drafted in euro.

Beneficiaries with accounting established in a currency other than the euro must convert the costs recorded in their accounts into euro, at the average of the daily exchange rates published in the C series of the *Official Journal of the European Union*, calculated over the corresponding reporting period.

If no daily euro exchange rate is published in the *Official Journal of the European Union* for the currency in question, they must be converted at the average of the monthly accounting rates published on the Commission's website, calculated over the corresponding reporting period.

Beneficiaries with accounting established in euro must convert costs incurred in another currency into euro according to their usual accounting practices.

20.7 Language of reports

All reports (technical and financial reports, including financial statements) must be submitted in the language of the Agreement.

20.8 Consequences of non-compliance — Suspension of the payment deadline — Termination

If the reports submitted do not comply with this Article, the *Commission* may suspend the payment deadline (see Article 47) and apply any of the other measures described in Chapter 6.

If the coordinator breaches its obligation to submit the reports and if it fails to comply with this obligation within 30 days following a written reminder sent by the *Commission*, the Agreement may be terminated (see Article 50).

ARTICLE 21 — PAYMENTS AND PAYMENT ARRANGEMENTS

21.1 Payments to be made

The following payments will be made to the coordinator:

- one **pre-financing payment**;

- one or more **interim payments**, on the basis of the request(s) for interim payment (see Article 20), and

- one **payment of the balance**, on the basis of the request for payment of the balance (see Article 20).

21.2 Pre-financing payment — Amount — Amount retained for the Guarantee Fund

The aim of the pre-financing is to provide the beneficiaries with a float.

It remains the property of the *EU* until the payment of the balance.

The amount of the pre-financing payment will be EUR **3,248,708.12** (three million two hundred and forty eight thousand seven hundred and eight EURO and twelve eurocents).

The *Commission* will — except if Article 48 applies — make the pre-financing payment to the coordinator within 30 days either from the entry into force of the Agreement (see Article 58) or from 10 days before the starting date of the action (see Article 3), whichever is the latest.

An amount of EUR **249,900.63** (two hundred and forty nine thousand nine hundred EURO and sixty three eurocents), corresponding to 5% of the maximum grant amount (see Article 5.1), is retained by the *Commission* from the pre-financing payment and transferred into the '**Guarantee Fund**'.

21.3 Interim payments — Amount — Calculation

Interim payments reimburse the eligible costs incurred for the implementation of the action during the corresponding reporting periods.

The *Commission* will pay to the coordinator the amount due as interim payment within 90 days from receiving the periodic report (see Article 20.3), except if Articles 47 or 48 apply.

Payment is subject to the approval of the periodic report. Its approval does not imply recognition of the compliance, authenticity, completeness or correctness of its content.

The **amount due as interim payment** is calculated by the *Commission* in the following steps:

Step 1 – Application of the reimbursement rates

Step 2 – Limit to 90% of the maximum grant amount

21.3.1 Step 1 — Application of the reimbursement rates

The reimbursement rate(s) (see Article 5.2) are applied to the eligible costs (actual costs, unit costs and flat-rate costs ; see Article 6) declared by the beneficiaries (see Article 20) and approved by the *Commission* (see above) for the concerned reporting period.

21.3.2 Step 2 — Limit to 90% of the maximum grant amount

The total amount of pre-financing and interim payments must not exceed 90% of the maximum grant amount set out in Article 5.1. The maximum amount for the interim payment will be calculated as follows:

{90% of the maximum grant amount (see Article 5.1)

minus

{pre-financing and previous interim payments}}.

21.4 Payment of the balance — Amount — Calculation — Release of the amount retained for the Guarantee Fund

The payment of the balance reimburses the remaining part of the eligible costs incurred by the beneficiaries for the implementation of the action.

If the total amount of earlier payments is greater than the final grant amount (see Article 5.3), the payment of the balance takes the form of a recovery (see Article 44).

If the total amount of earlier payments is lower than the final grant amount, the *Commission* will pay the balance within 90 days from receiving the final report (see Article 20.4), except if Articles 47 or 48 apply.

Payment is subject to the approval of the final report. Its approval does not imply recognition of the compliance, authenticity, completeness or correctness of its content.

The **amount due as the balance** is calculated by the *Commission* by deducting the total amount of pre-financing and interim payments (if any) already made, from the final grant amount determined in accordance with Article 5.3:

{final grant amount (see Article 5.3)

minus

{pre-financing and interim payments (if any) made}}.

At the payment of the balance, the amount retained for the Guarantee Fund (see above) will be released and:

- if the balance is positive: the amount released will be paid in full to the coordinator together with the amount due as the balance;

- if the balance is negative (payment of the balance taking the form of recovery): it will be deducted from the amount released (see Article 44.1.2). If the resulting amount:

    - is positive, it will be paid to the coordinator

    - is negative, it will be recovered.

The amount to be paid may however be offset — without the beneficiary's consent — against any other amount owed by the beneficiary to the Commission or an executive agency (under the EU or Euratom budget), up to the maximum EU contribution indicated, for that beneficiary, in the estimated budget (see Annex 2).

21.5 Notification of amounts due

When making payments, the *Commission* will formally notify to the coordinator the amount due, specifying whether it concerns an interim payment or the payment of the balance.

For the payment of the balance, the notification will also specify the final grant amount.

In the case of reduction of the grant or recovery of undue amounts, the notification will be preceded by the contradictory procedure set out in Articles 43 and 44.

21.6 Currency for payments

The *Commission* will make all payments in euro.

21.7 Payments to the coordinator — Distribution to the beneficiaries

Payments will be made to the coordinator.

Payments to the coordinator will discharge the *Commission* from its payment obligation.

The coordinator must distribute the payments between the beneficiaries without unjustified delay.

Pre-financing may however be distributed only:

(a) if the minimum number of beneficiaries set out in the call for proposals has acceded to the Agreement (see Article 56) and

(b) to beneficiaries that have acceded to the Agreement (see Article 56).

21.8 Bank account for payments

All payments will be made to the following bank account:

Name of bank: LLOYDS BANK PLC
Address of branch: SHEFFIELD, United Kingdom
Full name of the account holder: THE UNIVERSITY OF SHEFFIELD HORIZON2020
Full account number (including bank codes):
IBAN code: GB40LOYD30975186497636

21.9 Costs of payment transfers

The cost of the payment transfers is borne as follows:

- the *Commission* bears the cost of transfers charged by its bank;
- the beneficiary bears the cost of transfers charged by its bank;
- the party causing a repetition of a transfer bears all costs of the repeated transfer.

21.10 Date of payment

Payments by the *Commission* are considered to have been carried out on the date when they are debited to its account.

21.11 Consequences of non-compliance

21.11.1 If the *Commission* does not pay within the payment deadlines (see above), the beneficiaries are entitled to **late-payment interest** at the rate applied by the European Central Bank (ECB) for its main refinancing operations in euros ('reference rate'), plus three and a half points. The reference rate is the rate in force on the first day of the month in which the payment deadline expires, as published in the C series of the *Official Journal of the European Union*.

If the late-payment interest is lower than or equal to EUR 200, it will be paid to the coordinator only upon request submitted within two months of receiving the late payment.

Late-payment interest is not due if all beneficiaries are EU Member States (including regional and local government authorities or other public bodies acting on behalf of a Member State for the purpose of this Agreement).

Suspension of the payment deadline or payments (see Articles 47 and 48) will not be considered as late payment.

Late-payment interest covers the period running from the day following the due date for payment (see above), up to and including the date of payment.

Late-payment interest is not considered for the purposes of calculating the final grant amount.

21.11.2 If the coordinator breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or the participation of the coordinator may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 22 — CHECKS, REVIEWS, AUDITS AND INVESTIGATIONS — EXTENSION OF FINDINGS

22.1 Checks, reviews and audits by the Commission

22.1.1 Right to carry out checks

The Commission will — during the implementation of the action or afterwards — check the proper implementation of the action and compliance with the obligations under the Agreement, including assessing deliverables and reports.

For this purpose the Commission may be assisted by external persons or bodies.

The Commission may also request additional information in accordance with Article 17. The Commission may request beneficiaries to provide such information to it directly.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

22.1.2 Right to carry out reviews

The Commission may — during the implementation of the action or afterwards — carry out reviews on the proper implementation of the action (including assessment of deliverables and reports),

compliance with the obligations under the Agreement and continued scientific or technological relevance of the action.

Reviews may be started **up to two years after the payment of the balance**. They will be formally notified to the coordinator or beneficiary concerned and will be considered to have started on the date of the formal notification.

If the review is carried out on a third party (see Articles 10 to 16), the beneficiary concerned must inform the third party.

The Commission may carry out reviews directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the coordinator or beneficiary concerned of the identity of the external persons or bodies. They have the right to object to the appointment on grounds of commercial confidentiality.

The coordinator or beneficiary concerned must provide — within the deadline requested — any information and data in addition to deliverables and reports already submitted (including information on the use of resources). The Commission may request beneficiaries to provide such information to it directly.

The coordinator or beneficiary concerned may be requested to participate in meetings, including with external experts.

For **on-the-spot** reviews, the beneficiaries must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the review findings, a '**review report**' will be drawn up.

The Commission will formally notify the review report to the coordinator or beneficiary concerned, which has 30 days to formally notify observations ('**contradictory review procedure**').

Reviews (including review reports) are in the language of the Agreement.

22.1.3 Right to carry out audits

The Commission may — during the implementation of the action or afterwards — carry out audits on the proper implementation of the action and compliance with the obligations under the Agreement.

Audits may be started **up to two years after the payment of the balance**. They will be formally notified to the coordinator or beneficiary concerned and will be considered to have started on the date of the formal notification.

If the audit is carried out on a third party (see Articles 10 to 16), the beneficiary concerned must inform the third party.

The Commission may carry out audits directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the coordinator or beneficiary concerned of the

identity of the external persons or bodies. They have the right to object to the appointment on grounds of commercial confidentiality.

The coordinator or beneficiary concerned must provide — within the deadline requested — any information (including complete accounts, individual salary statements or other personal data) to verify compliance with the Agreement. The Commission may request beneficiaries to provide such information to it directly.

For **on-the-spot** audits, the beneficiaries must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the audit findings, a '**draft audit report**' will be drawn up.

The Commission will formally notify the draft audit report to the coordinator or beneficiary concerned, which has 30 days to formally notify observations ('**contradictory audit procedure**'). This period may be extended by the Commission in justified cases.

The '**final audit report**' will take into account observations by the coordinator or beneficiary concerned. The report will be formally notified to it.

Audits (including audit reports) are in the language of the Agreement.

The Commission may also access the beneficiaries' statutory records for the periodical assessment of unit costs or flat-rate amounts.

22.2 Investigations by the European Anti-Fraud Office (OLAF)

Under Regulations No 883/2013[15] and No 2185/96[16] (and in accordance with their provisions and procedures), the European Anti-Fraud Office (OLAF) may — at any moment during implementation of the action or afterwards — carry out investigations, including on-the-spot checks and inspections, to establish whether there has been fraud, corruption or any other illegal activity affecting the financial interests of the EU.

22.3 Checks and audits by the European Court of Auditors (ECA)

Under Article 287 of the Treaty on the Functioning of the European Union (TFEU) and Article 161 of the Financial Regulation No 966/2012[17], the European Court of Auditors (ECA) may — at any moment during implementation of the action or afterwards — carry out audits.

[15] Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council of 11 September 2013 concerning investigations conducted by the European Anti-Fraud Office (OLAF) and repealing Regulation (EC) No 1073/1999 of the European Parliament and of the Council and Council Regulation (Euratom) No 1074/1999 (OJ L 248, 18.09.2013, p. 1).

[16] Council Regulation (Euratom, EC) No 2185/1996 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15.11.1996, p. 2).

[17] Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council of 25 October 2012 on the financial rules applicable to the general budget of the Union and repealing Council Regulation (EC, Euratom) No 1605/2002 (OJ L 298, 26.10.2012, p. 1).

The ECA has the right of access for the purpose of checks and audits.

22.4 Checks, reviews, audits and investigations for international organisations

Not applicable

22.5 Consequences of findings in checks, reviews, audits and investigations — Extension of findings

22.5.1 Findings in this grant

Findings in checks, reviews, audits or investigations carried out in the context of this grant may lead to the rejection of ineligible costs (see Article 42), reduction of the grant (see Article 43), recovery of undue amounts (see Article 44) or to any of the other measures described in Chapter 6.

Rejection of costs or reduction of the grant after the payment of the balance will lead to a revised final grant amount (see Article 5.4).

Findings in checks, reviews, audits or investigations may lead to a request for amendment for the modification of Annex 1 (see Article 55).

Checks, reviews, audits or investigations that find systemic or recurrent errors, irregularities, fraud or breach of obligations may also lead to consequences in other EU or Euratom grants awarded under similar conditions ('**extension of findings from this grant to other grants**').

Moreover, findings arising from an OLAF investigation may lead to criminal prosecution under national law.

22.5.2 Findings in other grants

The Commission may extend findings from other grants to this grant ('**extension of findings from other grants to this grant**'), if:

(a) the beneficiary concerned is found, in other EU or Euratom grants awarded under similar conditions, to have committed systemic or recurrent errors, irregularities, fraud or breach of obligations that have a material impact on this grant and

(b) those findings are formally notified to the beneficiary concerned — together with the list of grants affected by the findings — no later than two years after the payment of the balance of this grant.

The extension of findings may lead to the rejection of costs (see Article 42), reduction of the grant (see Article 43), recovery of undue amounts (see Article 44), suspension of payments (see Article 48), suspension of the action implementation (see Article 49) or termination (see Article 50).

22.5.3 Procedure

The Commission will formally notify the beneficiary concerned the systemic or recurrent errors and its intention to extend these audit findings, together with the list of grants affected.

22.5.3.1 If the findings concern **eligibility of costs**: the formal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings;

(b) the request to submit **revised financial statements** for all grants affected;

(c) the **correction rate for extrapolation** established by the Commission on the basis of the systemic or recurrent errors, to calculate the amounts to be rejected if the beneficiary concerned:

(i) considers that the submission of revised financial statements is not possible or practicable or

(ii) does not submit revised financial statements.

The beneficiary concerned has 90 days from receiving notification to submit observations, revised financial statements or to propose a duly substantiated **alternative correction method**. This period may be extended by the Commission in justified cases.

The amounts to be rejected will be determined on the basis of the revised financial statements, subject to their approval.

If the Commission does not receive any observations or revised financial statements, does not accept the observations or the proposed alternative correction method or does not approve the revised financial statements, it will formally notify the beneficiary concerned the application of the initially notified correction rate for extrapolation.

If the Commission accepts the alternative correction method proposed by the beneficiary concerned, it will formally notify the application of the accepted alternative correction method.

22.5.3.2 If the findings concern **improper implementation** or a **breach of another obligation**: the formal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings and

(b) the flat-rate the Commission intends to apply according to the principle of proportionality.

The beneficiary concerned has 90 days from receiving notification to submit observations or to propose a duly substantiated alternative flat-rate.

If the Commission does not receive any observations or does not accept the observations or the proposed alternative flat-rate, it will formally notify the beneficiary concerned the application of the initially notified flat-rate.

If the Commission accepts the alternative flat-rate proposed by the beneficiary concerned, it will formally notify the application of the accepted alternative flat-rate.

22.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, any insufficiently substantiated costs will be ineligible (see Article 6) and will be rejected (see Article 42).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 23 — EVALUATION OF THE IMPACT OF THE ACTION

23.1 Right to evaluate the impact of the action

The Commission may carry out interim and final evaluations of the impact of the action measured against the objective of the *EU* programme.

Evaluations may be started during implementation of the action and up to *five* years after the payment of the balance. The evaluation is considered to start on the date of the formal notification to the coordinator or beneficiaries.

The Commission may make these evaluations directly (using its own staff) or indirectly (using external bodies or persons it has authorised to do so).

The coordinator or beneficiaries must provide any information relevant to evaluate the impact of the action, including information in electronic format.

23.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the *Commission* may apply the measures described in Chapter 6.

SECTION 3 RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND AND RESULTS

SUBSECTION 1 GENERAL

ARTICLE 23a — MANAGEMENT OF INTELLECTUAL PROPERTY

23a.1 Obligation to take measures to implement the Commission Recommendation on the management of intellectual property in knowledge transfer activities

Beneficiaries that are universities or other public research organisations must take measures to implement the principles set out in Points 1 and 2 of the Code of Practice annexed to the Commission Recommendation on the management of intellectual property in knowledge transfer activities[18].

This does not change the obligations set out in Subsections 2 and 3 of this Section.

The beneficiaries must ensure that researchers and third parties involved in the action are aware of them.

23a.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the *Commission* may apply any of the measures described in Chapter 6.

[18] Commission Recommendation C (2008) 1329 of 10.4.2008 on the management of intellectual property in knowledge transfer activities and the Code of Practice for universities and other public research institutions attached to this recommendation.

SUBSECTION 2 RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND

ARTICLE 24 — AGREEMENT ON BACKGROUND

24.1 Agreement on background

The beneficiaries must identify and agree (in writing) on the background for the action ('**agreement on background**').

'**Background**' means any data, know-how or information — whatever its form or nature (tangible or intangible), including any rights such as intellectual property rights — that:

(a) is held by the beneficiaries before they acceded to the Agreement, and

(b) is needed to implement the action or exploit the results.

24.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 25 — ACCESS RIGHTS TO BACKGROUND

25.1 Exercise of access rights — Waiving of access rights — No sub-licensing

To exercise access rights, this must first be requested in writing ('**request for access**').

'**Access rights**' means rights to use results or background under the terms and conditions laid down in this Agreement.

Waivers of access rights are not valid unless in writing.

Unless agreed otherwise, access rights do not include the right to sub-license.

25.2 Access rights for other beneficiaries, for implementing their own tasks under the action

The beneficiaries must give each other access — on a royalty-free basis — to background needed to implement their own tasks under the action, unless the beneficiary that holds the background has — before acceding to the Agreement —:

(a) informed the other beneficiaries that access to its background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel), or

(b) agreed with the other beneficiaries that access would not be on a royalty-free basis.

25.3 Access rights for other beneficiaries, for exploiting their own results

The beneficiaries must give each other access — under fair and reasonable conditions — to background needed for exploiting their own results, unless the beneficiary that holds the background has — before acceding to the Agreement — informed the other beneficiaries that access to its

background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel).

'**Fair and reasonable conditions**' means appropriate conditions, including possible financial terms or royalty-free conditions, taking into account the specific circumstances of the request for access, for example the actual or potential value of the results or background to which access is requested and/or the scope, duration or other characteristics of the exploitation envisaged.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

25.4 Access rights for affiliated entities

Unless otherwise agreed in the consortium agreement, access to background must also be given — under fair and reasonable conditions (see above; Article 25.3) and unless it is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel) — to affiliated entities[19] established in an EU Member State or '**associated country**'[20], if this is needed to exploit the results generated by the beneficiaries to which they are affiliated.

Unless agreed otherwise (see above; Article 25.1), the affiliated entity concerned must make the request directly to the beneficiary that holds the background.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

25.5 Access rights for third parties

Not applicable

25.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

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[19] For the definition, see Article 2.1(2) of the Rules for Participation Regulation No 1290/2013: '**affiliated entity**' means any legal entity that is under the direct or indirect control of a participant, or under the same direct or indirect control as the participant, or that is directly or indirectly controlling a participant.
'Control' may take any of the following forms:
(a) the direct or indirect holding of more than 50% of the nominal value of the issued share capital in the legal entity concerned, or of a majority of the voting rights of the shareholders or associates of that entity;
(b) the direct or indirect holding, in fact or in law, of decision-making powers in the legal entity concerned.
However the following relationships between legal entities shall not in themselves be deemed to constitute controlling relationships:
(a) the same public investment corporation, institutional investor or venture-capital company has a direct or indirect holding of more than 50% of the nominal value of the issued share capital or a majority of voting rights of the shareholders or associates;
(b) the legal entities concerned are owned or supervised by the same public body.

[20] For the definition, see Article 2.1(3) of the Rules for Participation Regulation No 1290/2013: '**associated country**' means a third country which is party to an international agreement with the Union, as identified in *Article 7 of Horizon 2020 Framework Programme Regulation No 1291/2013. Article 7 sets out the conditions for association of non-EU countries to Horizon 2020.*

SUBSECTION 3 RIGHTS AND OBLIGATIONS RELATED TO RESULTS

ARTICLE 26 — OWNERSHIP OF RESULTS

26.1 Ownership by the beneficiary that generates the results

Results are owned by the beneficiary that generates them.

'**Results**' means any (tangible or intangible) output of the action such as data, knowledge or information — whatever its form or nature, whether it can be protected or not — that is generated in the action, as well as any rights attached to it, including intellectual property rights.

26.2 Joint ownership by several beneficiaries

Two or more beneficiaries own results jointly if:

(a) they have jointly generated them and

(b) it is not possible to:

(i) establish the respective contribution of each beneficiary, or

(ii) separate them for the purpose of applying for, obtaining or maintaining their protection (see Article 27).

The joint owners must agree (in writing) on the allocation and terms of exercise of their joint ownership ('**joint ownership agreement**'), to ensure compliance with their obligations under this Agreement.

Unless otherwise agreed in the joint ownership agreement, each joint owner may grant non-exclusive licences to third parties to exploit jointly-owned results (without any right to sub-license), if the other joint owners are given:

(a) at least 45 days advance notice and

(b) fair and reasonable compensation.

Once the results have been generated, joint owners may agree (in writing) to apply another regime than joint ownership (such as, for instance, transfer to a single owner (see Article 30) with access rights for the others).

26.3 Rights of third parties (including personnel)

If third parties (including personnel) may claim rights to the results, the beneficiary concerned must ensure that it complies with its obligations under the Agreement.

If a third party generates results, the beneficiary concerned must obtain all necessary rights (transfer, licences or other) from the third party, in order to be able to respect its obligations as if those results were generated by the beneficiary itself.

If obtaining the rights is impossible, the beneficiary must refrain from using the third party to generate the results.

26.4 *EU* ownership, to protect results

26.4.1 *The EU* may — with the consent of the beneficiary concerned — assume ownership of results to protect them, if a beneficiary intends — up to four years after the period set out in Article 3 — to disseminate its results without protecting them, except in any of the following cases:

(a) the lack of protection is because protecting the results is not possible, reasonable or justified (given the circumstances);

(b) the lack of protection is because there is a lack of potential for commercial or industrial exploitation, or

(c) the beneficiary intends to transfer the results to another beneficiary or third party established in an EU Member State or associated country, which will protect them.

Before the results are disseminated and unless any of the cases above under Points (a), (b) or (c) applies, the beneficiary must formally notify the *Commission* and at the same time inform it of any reasons for refusing consent. The beneficiary may refuse consent only if it can show that its legitimate interests would suffer significant harm.

If the *Commission* decides to assume ownership, it will formally notify the beneficiary concerned within 45 days of receiving notification.

No dissemination relating to these results may before the end of this period or, if the *Commission* takes a positive decision, until it has taken the necessary steps to protect the results.

26.4.2 *The EU* may — with the consent of the beneficiary concerned — assume ownership of results to protect them, if a beneficiary intends — up to four years after the period set out in Article 3 — to stop protecting them or not to seek an extension of protection, except in any of the following cases:

(a) the protection is stopped because of a lack of potential for commercial or industrial exploitation;

(b) an extension would not be justified given the circumstances.

A beneficiary that intends to stop protecting results or not seek an extension must — unless any of the cases above under Points (a) or (b) applies — formally notify the *Commission* at least 60 days before the protection lapses or its extension is no longer possible and at the same time inform it of any reasons for refusing consent. The beneficiary may refuse consent only if it can show that its legitimate interests would suffer significant harm.

If the *Commission* decides to assume ownership, it will formally notify the beneficiary concerned within 45 days of receiving notification.

26.5 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to the any of the other measures described in Chapter 6.

ARTICLE 27 — PROTECTION OF RESULTS — VISIBILITY OF EU FUNDING

27.1 Obligation to protect the results

Each beneficiary must examine the possibility of protecting its results and must adequately protect them — for an appropriate period and with appropriate territorial coverage — if:

(a) the results can reasonably be expected to be commercially or industrially exploited and

(b) protecting them is possible, reasonable and justified (given the circumstances).

When deciding on protection, the beneficiary must consider its own legitimate interests and the legitimate interests (especially commercial) of the other beneficiaries.

27.2 *EU* ownership, to protect the results

If a beneficiary intends not to protect its results, to stop protecting them or not seek an extension of protection, *The EU* may — under certain conditions (see Article 26.4) — assume ownership to ensure their (continued) protection.

27.3 Information on EU funding

Applications for protection of results (including patent applications) filed by or on behalf of a beneficiary must — unless the *Commission* requests or agrees otherwise or unless it is impossible — include the following:

> "The project leading to this application has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 689617".

27.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 28 — EXPLOITATION OF RESULTS

28.1 Obligation to exploit the results

Each beneficiary must — up to four years after the period set out in Article 3 — take measures aiming to ensure '**exploitation**' of its results (either directly or indirectly, in particular through transfer or licensing; see Article 30) by:

(a) using them in further research activities (outside the action);

(b) developing, creating or marketing a product or process;

(c) creating and providing a service, or

(d) using them in standardisation activities.

This does not change the security obligations in Article 37, which still apply.

28.2 Results that could contribute to European or international standards — Information on EU funding

If results are incorporated in a standard, the beneficiary concerned must — unless the *Commission* requests or agrees otherwise or unless it is impossible — ask the standardisation body to include the following statement in (information related to) the standard:

> "Results incorporated in this standard received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 689617".

28.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced in accordance with Article 43.

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 29 — DISSEMINATION OF RESULTS — OPEN ACCESS — VISIBILITY OF EU FUNDING

29.1 Obligation to disseminate results

Unless it goes against their legitimate interests, each beneficiary must — as soon as possible — '**disseminate**' its results by disclosing them to the public by appropriate means (other than those resulting from protecting or exploiting the results), including in scientific publications (in any medium).

This does not change the obligation to protect results in Article 27, the confidentiality obligations in Article 36, the security obligations in Article 37 or the obligations to protect personal data in Article 39, all of which still apply.

A beneficiary that intends to disseminate its results must give advance notice to the other beneficiaries of — unless agreed otherwise — at least 45 days, together with sufficient information on the results it will disseminate.

Any other beneficiary may object within — unless agreed otherwise — 30 days of receiving notification, if it can show that its legitimate interests in relation to the results or background would be significantly harmed. In such cases, the dissemination may not take place unless appropriate steps are taken to safeguard these legitimate interests.

If a beneficiary intends not to protect its results, it may — under certain conditions (see Article 26.4.1) — need to formally notify the *Commission* before dissemination takes place.

29.2 Open access to scientific publications

Each beneficiary must ensure open access (free of charge online access for any user) to all peer-reviewed scientific publications relating to its results.

In particular, it must:

(a) as soon as possible and at the latest on publication, deposit a machine-readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications;

Moreover, the beneficiary must aim to deposit at the same time the research data needed to validate the results presented in the deposited scientific publications.

(b) ensure open access to the deposited publication — via the repository — at the latest:

(i) on publication, if an electronic version is available for free via the publisher, or

(ii) within six months of publication (twelve months for publications in the social sciences and humanities) in any other case.

(c) ensure open access — via the repository — to the bibliographic metadata that identify the deposited publication.

The bibliographic metadata must be in a standard format and must include all of the following:

- the terms *"European Union (EU)" and "Horizon 2020"*;
- the name of the action, acronym and grant number;
- the publication date, and length of embargo period if applicable, and
- a persistent identifier.

29.3 Open access to research data

Not applicable

29.4 Information on EU funding — Obligation and right to use the EU emblem

Unless the *Commission* requests or agrees otherwise or unless it is impossible, any dissemination of results (in any form, including electronic) must:

(a) display the EU emblem and

(b) include the following text:

"This project has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 689617".

When displayed together with another logo, the EU emblem must have appropriate prominence.

For the purposes of their obligations under this Article, the beneficiaries may use the EU emblem without first obtaining approval from the *Commission*.

This does not however give them the right to exclusive use.

Moreover, they may not appropriate the EU emblem or any similar trademark or logo, either by registration or by any other means.

29.5 Disclaimer excluding *Commission* responsibility

Any dissemination of results must indicate that it reflects only the author's view and that the *Commission* is not responsible for any use that may be made of the information it contains.

29.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 30 — TRANSFER AND LICENSING OF RESULTS

30.1 Transfer of ownership

Each beneficiary may transfer ownership of its results.

It must however ensure that its obligations under Articles 26.2, 26.4, 27, 28, 29, 30 and 31 also apply to the new owner and that this owner has the obligation to pass them on in any subsequent transfer.

This does not change the security obligations in Article 37, which still apply.

Unless agreed otherwise (in writing) for specifically-identified third parties or unless impossible under applicable EU and national laws on mergers and acquisitions, a beneficiary that intends to transfer ownership of results must give at least 45 days advance notice (or less if agreed in writing) to the other beneficiaries that still have (or still may request) access rights to the results. This notification must include sufficient information on the new owner to enable any beneficiary concerned to assess the effects on its access rights.

Unless agreed otherwise (in writing) for specifically-identified third parties, any other beneficiary may object within 30 days of receiving notification (or less if agreed in writing), if it can show that the transfer would adversely affect its access rights. In this case, the transfer may not take place until agreement has been reached between the beneficiaries concerned.

30.2 Granting licenses

Each beneficiary may grant licences to its results (or otherwise give the right to exploit them), if:

(a) this does not impede the rights under Article 31 and

(b) *not applicable.*

In addition to Points (a) and (b), exclusive licences for results may be granted only if all the other beneficiaries concerned have waived their access rights (see Article 31.1).

This does not change the dissemination obligations in Article 29 or security obligations in Article 37, which still apply.

30.3 *Commission* right to object to transfers or licensing

Not applicable

30.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 31 — ACCESS RIGHTS TO RESULTS

31.1 Exercise of access rights — Waiving of access rights — No sub-licensing

The conditions set out in Article 25.1 apply.

The obligations set out in this Article do not change the security obligations in Article 37, which still apply.

31.2 Access rights for other beneficiaries, for implementing their own tasks under the action

The beneficiaries must give each other access — on a royalty-free basis — to results needed for implementing their own tasks under the action.

31.3 Access rights for other beneficiaries, for exploiting their own results

The beneficiaries must give each other — under fair and reasonable conditions (see Article 25.3) — access to results needed for exploiting their own results.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

31.4 Access rights of affiliated entities

Unless agreed otherwise in the consortium agreement, access to results must also be given — under fair and reasonable conditions (Article 25.3) — to affiliated entities established in an EU Member State or associated country, if this is needed for those entities to exploit the results generated by the beneficiaries to which they are affiliated.

Unless agreed otherwise (see above; Article 31.1), the affiliated entity concerned must make any such request directly to the beneficiary that owns the results.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

31.5 Access rights for the EU institutions, bodies, offices or agencies and EU Member States

The beneficiaries must give access to their results — on a royalty-free basis — to EU institutions, bodies, offices or agencies, for developing, implementing or monitoring EU policies or programmes.

Such access rights are limited to non-commercial and non-competitive use.

This does not change the right to use any material, document or information received from the beneficiaries for communication and publicising activities (see Article 38.2).

31.6 Access rights for third parties

Not applicable

31.7 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

SECTION 4 OTHER RIGHTS AND OBLIGATIONS

ARTICLE 32 — RECRUITMENT AND WORKING CONDITIONS FOR RESEARCHERS

32.1 Obligation to take measures to implement the European Charter for Researchers and Code of Conduct for the Recruitment of Researchers

The beneficiaries must take all measures to implement the principles set out in the Commission Recommendation on the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers[22], in particular regarding:

- working conditions;
- transparent recruitment processes based on merit, and
- career development.

The beneficiaries must ensure that researchers and third parties involved in the action are aware of them.

32.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the *Commission* may apply any of the measures described in Chapter 6.

ARTICLE 33 — GENDER EQUALITY

33.1 Obligation to aim for gender equality

The beneficiaries must take all measures to promote equal opportunities between men and women in the implementation of the action. They must aim, to the extent possible, for a gender balance at all levels of personnel assigned to the action, including at supervisory and managerial level.

33.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the *Commission* may apply any of the measures described in Chapter 6.

[22] Commission Recommendation 2005/251/EC of 11 March 2005 on the European Charter for Researchers and on a Code of Conduct for the Recruitment of Researchers (OJ L 75, 22.3.2005, p. 67).

ARTICLE 34 — ETHICS

34.1 Obligation to comply with ethical principles

The beneficiaries must carry out the action in compliance with:

(a) ethical principles (including the highest standards of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity[23] — and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct) and

(b) applicable international, EU and national law.

Funding will not be granted for activities carried out outside the EU if they are prohibited in all Member States.

The beneficiaries must ensure that the activities under the action have an exclusive focus on civil applications.

The beneficiaries must ensure that the activities under the action do not:

(a) aim at human cloning for reproductive purposes;

(b) intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or

(c) intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

34.2 Activities raising ethical issues

Activities raising ethical issues must comply with the '**ethics requirements**' set out in Annex 1.

Before the beginning of an activity raising an ethical issue, the coordinator must submit (see Article 52) to the *Commission* copy of:

(a) any ethics committee opinion required under national law and

(b) any notification or authorisation for activities raising ethical issues required under national law.

If these documents are not in English, the coordinator must also submit an English summary of the submitted opinions, notifications and authorisations (containing, if available, the conclusions of the committee or authority concerned).

If these documents are specifically requested for the action, the request must contain an explicit reference to the action title. The coordinator must submit a declaration by each beneficiary concerned that all the submitted documents cover the action tasks.

[23] The European Code of Conduct for Research Integrity of ALLEA (All European Academies) and ESF (European Science Foundation) of March 2011.
http://www.esf.org/fileadmin/Public_documents/Publications/Code_Conduct_ResearchIntegrity.pdf

34.3 Activities involving human embryos or human embryonic stem cells

Activities involving research on human embryos or human embryonic stem cells may be carried out only if:

- they are set out in Annex 1 or
- the coordinator has obtained explicit approval (in writing) from the *Commission* (see Article 52).

34.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or participation of the beneficiary may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 35 — CONFLICT OF INTERESTS

35.1 Obligation to avoid a conflict of interests

The beneficiaries must take all measures to prevent any situation where the impartial and objective implementation of the action is compromised for reasons involving economic interest, political or national affinity, family or emotional ties or any other shared interest (‘**conflict of interests**’).

They must formally notify to the *Commission* without delay any situation constituting or likely to lead to a conflict of interests and immediately take all the necessary steps to rectify this situation.

The *Commission* may verify that the measures taken are appropriate and may require additional measures to be taken by a specified deadline.

35.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or participation of the beneficiary may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 36 — CONFIDENTIALITY

36.1 General obligation to maintain confidentiality

During implementation of the action and for four years after the period set out in Article 3, the parties must keep confidential any data, documents or other material (in any form) that is identified as confidential at the time it is disclosed (‘**confidential information**’).

If a beneficiary requests, the *Commission* may agree to keep such information confidential for an additional period beyond the initial four years.

If information has been identified as confidential only orally, it will be considered to be confidential only if this is confirmed in writing within 15 days of the oral disclosure.

Unless otherwise agreed between the parties, they may use confidential information only to implement the Agreement.

The beneficiaries may disclose confidential information to their personnel or third parties involved in the action only if they:

(a) need to know to implement the Agreement and

(b) are bound by an obligation of confidentiality.

This does not change the security obligations in Article 37, which still apply.

The *Commission* may disclose confidential information to its staff, other EU institutions and bodies or third parties, if:

(a) this is necessary to implement the Agreement or safeguard the EU's financial interests and

(b) the recipients of the information are bound by an obligation of confidentiality.

Under the conditions set out in Article 4 of the Rules for Participation Regulation No 1290/2013[24], the Commission must moreover make available information on the results to other EU institutions, bodies, offices or agencies as well as Member States or associated countries.

The confidentiality obligations no longer apply if:

(a) the disclosing party agrees to release the other party;

(b) the information was already known by the recipient or is given to him without obligation of confidentiality by a third party that was not bound by any obligation of confidentiality;

(c) the recipient proves that the information was developed without the use of confidential information;

(d) the information becomes generally and publicly available, without breaching any confidentiality obligation, or

(e) the disclosure of the information is required by EU or national law.

36.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

[24] Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" (OJ L 347, 20.12.2013 p.81).

ARTICLE 37 — SECURITY-RELATED OBLIGATIONS

37.1 Results with a security recommendation

Not applicable

37.2 Classified results

Not applicable

37.3 Activities involving dual-use goods or dangerous materials and substances

Not applicable

37.4 Consequences of non-compliance

Not applicable

ARTICLE 38 — PROMOTING THE ACTION — VISIBILITY OF EU FUNDING

38.1 Communication activities by beneficiaries

38.1.1 Obligation to promote the action and its results

The beneficiaries must promote the action and its results, by providing targeted information to multiple audiences (including the media and the public) in a strategic and effective manner.

This does not change the dissemination obligations in Article 29, the confidentiality obligations in Article 36 or the security obligations in Article 37, all of which still apply.

Before engaging in a communication activity expected to have a major media impact, the beneficiaries must inform the *Commission* (see Article 52).

38.1.2 Information on EU funding — Obligation and right to use the EU emblem

Unless the *Commission* requests or agrees otherwise or unless it is impossible, any communication activity related to the action (including in electronic form, via social media, etc.) and any infrastructure, equipment and major results funded by the grant must:

(a) display the EU emblem and

(b) include the following text:

> For communication activities: "This project has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 689617".
>
> For infrastructure, equipment and major results: "This *[infrastructure][equipment][insert type of result]* is part of a project that has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 689617".

When displayed together with another logo, the EU emblem must have appropriate prominence.

For the purposes of their obligations under this Article, the beneficiaries may use the EU emblem without first obtaining approval from the *Commission*.

This does not, however, give them the right to exclusive use.

Moreover, they may not appropriate the EU emblem or any similar trademark or logo, either by registration or by any other means.

38.1.3 Disclaimer excluding the *Commission* responsibility

Any communication activity related to the action must indicate that it reflects only the author's view and that the *Commission* is not responsible for any use that may be made of the information it contains.

38.2 Communication activities by the *Commission*

38.2.1 Right to use beneficiaries' materials, documents or information

The *Commission* may use, for its communication and publicising activities, information relating to the action, documents notably summaries for publication and public deliverables as well as any other material, such as pictures or audio-visual material that it receives from any beneficiary (including in electronic form).

This does not change the confidentiality obligations in Article 36 and the security obligations in Article 37, all of which still apply.

However, if the *Commission's* use of these materials, documents or information would risk compromising legitimate interests, the beneficiary concerned may request the *Commission* not to use it (see Article 52).

The right to use a beneficiary's materials, documents and information includes:

(a) **use for its own purposes** (in particular, making them available to persons working for the *Commission* or any other EU institution, body, office or agency or body or institutions in EU Member States; and copying or reproducing them in whole or in part, in unlimited numbers);

(b) **distribution to the public** (in particular, publication as hard copies and in electronic or digital format, publication on the internet, as a downloadable or non-downloadable file, broadcasting by any channel, public display or presentation, communicating through press information services, or inclusion in widely accessible databases or indexes);

(c) **editing or redrafting** for communication and publicising activities (including shortening, summarising, inserting other elements (such as meta-data, legends, other graphic, visual, audio or text elements), extracting parts (e.g. audio or video files), dividing into parts, use in a compilation);

(d) **translation**;

(e) giving **access in response to individual requests** under Regulation No 1049/2001[25], without the right to reproduce or exploit;

[25] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ L 145, 31.5.2001, p. 43.

(f) **storage** in paper, electronic or other form;

(g) **archiving**, in line with applicable document-management rules, and

(h) the right to authorise **third parties** to act on its behalf or sub-license the modes of use set out in Points (b),(c),(d) and (f) to third parties if needed for the communication and publicising activities of the *Commission*.

If the right of use is subject to rights of a third party (including personnel of the beneficiary), the beneficiary must ensure that it complies with its obligations under this Agreement (in particular, by obtaining the necessary approval from the third parties concerned).

Where applicable (and if provided by the beneficiaries), the *Commission* will insert the following information:

> "© – [year] – [name of the copyright owner]. All rights reserved. Licensed to the *European Union (EU)* under conditions."

38.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 39 — PROCESSING OF PERSONAL DATA

39.1 Processing of personal data by the Commission

Any personal data under the Agreement will be processed by the Commission under Regulation No 45/2001[26] and according to the 'notifications of the processing operations' to the Data Protection Officer (DPO) of the Commission (publicly accessible in the DPO register).

Such data will be processed by the '**data controller**' of the Commission for the purposes of implementing, managing and monitoring the Agreement or protecting the financial interests of the EU or Euratom (including checks, reviews, audits and investigations; see Article 22).

The persons whose personal data are processed have the right to access and correct their own personal data. For this purpose, they must send any queries about the processing of their personal data to the data controller, via the contact point indicated in the 'service specific privacy statement(s) (SSPS)' that are published on the Commission websites.

They also have the right to have recourse at any time to the European Data Protection Supervisor (EDPS).

[26] Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data (OJ L 8, 12.01.2001, p. 1).

39.2 Processing of personal data by the beneficiaries

The beneficiaries must process personal data under the Agreement in compliance with applicable EU and national law on data protection (including authorisations or notification requirements).

The beneficiaries may grant their personnel access only to data that is strictly necessary for implementing, managing and monitoring the Agreement.

The beneficiaries must inform the personnel whose personal data are collected and processed by the Commission. For this purpose, they must provide them with the service specific privacy statement (SSPS) (see above), before transmitting their data to the Commission.

39.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under Article 39.2, the *Commission* may apply any of the measures described in Chapter 6.

ARTICLE 40 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE *COMMISSION*

The beneficiaries may not assign any of their claims for payment against the *Commission* to any third party, except if approved by the *Commission* on the basis of a reasoned, written request by the coordinator (on behalf of the beneficiary concerned).

If the *Commission* has not accepted the assignment or the terms of it are not observed, the assignment will have no effect on it.

In no circumstances will an assignment release the beneficiaries from their obligations towards the *Commission*.

CHAPTER 5 DIVISION OF BENEFICIARIES' ROLES AND RESPONSIBILITIES

ARTICLE 41 — DIVISION OF BENEFICIARIES' ROLES AND RESPONSIBILITIES

41.1 Roles and responsibilities towards the *Commission*

The beneficiaries have full responsibility for implementing the action and complying with the Agreement.

The beneficiaries are jointly and severally liable for the **technical implementation** of the action as described in Annex 1. If a beneficiary fails to implement its part of the action, the other beneficiaries become responsible for implementing this part (without being entitled to any additional EU funding for doing so), unless the *Commission* expressly relieves them of this obligation.

The **financial responsibility** of each beneficiary is governed by Articles 44, 45 and 46.

41.2 Internal division of roles and responsibilities

The internal roles and responsibilities of the beneficiaries are divided as follows:

(a) Each **beneficiary** must:

(i) keep information stored in the 'Beneficiary Register' (via the electronic exchange system) up to date (see Article 17);

(ii) inform the coordinator immediately of any events or circumstances likely to affect significantly or delay the implementation of the action (see Article 17);

(iii) submit to the coordinator in good time:

- individual financial statements for itself and, if required, certificates on the financial statements (see Article 20);
- the data needed to draw up the technical reports (see Article 20);
- ethics committee opinions and notifications or authorisations for activities raising ethical issues (see Article 34);
- any other documents or information required by the Commission under the Agreement, unless the Agreement requires the beneficiary to submit this information directly to the Commission.

(b) The **coordinator** must:

(i) monitor that the action is implemented properly (see Article 7);

(ii) act as the intermediary for all communications between the beneficiaries and the *Commission* (in particular, providing the *Commission* with the information described in Article 17), unless the Agreement specifies otherwise;

(iii) request and review any documents or information required by the *Commission* and verify their completeness and correctness before passing them on to the *Commission*;

(iv) submit the deliverables and reports to the *Commission* (see Articles 19 and 20);

(v) ensure that all payments are made to the other beneficiaries without unjustified delay (see Article 21);

(vi) inform the *Commission* of the amounts paid to each beneficiary, when required under the Agreement (see Articles 44 and 50) or requested by the *Commission*.

The coordinator may not delegate the above-mentioned tasks to any other beneficiary or subcontract them to any third party.

41.3 Internal arrangements between beneficiaries — Consortium agreement

*The beneficiaries must have internal arrangements regarding their operation and co-ordination to ensure that the action is implemented properly. These internal arrangements must be set out in a written '**consortium agreement**' between the beneficiaries, which may cover:*

- *internal organisation of the consortium;*

- *management of access to the electronic exchange system;*

- *distribution of EU funding;*

- *additional rules on rights and obligations related to background and results (including whether access rights remain or not, if a beneficiary is in breach of its obligations) (see Section 3 of Chapter 4);*

- *settlement of internal disputes;*

- *liability, indemnification and confidentiality arrangements between the beneficiaries.*

The consortium agreement must not contain any provision contrary to the Agreement.

41.4 Relationship with complementary beneficiaries — Collaboration agreement

Not applicable

41.5 Relationship with partners of a joint action — Coordination agreement

Not applicable

CHAPTER 6 REJECTION OF COSTS — REDUCTION OF THE GRANT — RECOVERY — PENALTIES — DAMAGES — SUSPENSION — TERMINATION — FORCE MAJEURE

SECTION 1 REJECTION OF COSTS — REDUCTION OF THE GRANT — RECOVERY — PENALTIES

ARTICLE 42 — REJECTION OF INELIGIBLE COSTS

42.1 Conditions

42.1.1 The *Commission* will — at the time of an **interim payment**, **at the payment of the balance** or **afterwards** — reject any costs which are ineligible (see Article 6), in particular following checks, reviews, audits or investigations (see Article 22).

42.1.2 The rejection may also be based on the **extension of findings from other grants to this grant**, under the conditions set out in Article 22.5.2.

42.2 Ineligible costs to be rejected — Calculation — Procedure

Ineligible costs will be rejected in full.

If the *Commission* rejects costs **without reduction of the grant** (see Article 43) or **recovery of undue amounts** (see Article 44), it will formally notify the coordinator or beneficiary concerned the rejection of costs, the amounts and the reasons why (if applicable, together with the notification of amounts due; see Article 21.5). The coordinator or beneficiary concerned may — within 30 days of receiving notification — formally notify the *Commission* of its disagreement and the reasons why.

If the *Commission* rejects costs **with reduction of the grant** or **recovery of undue amounts**, it will formally notify the rejection in the '**pre-information letter**' on reduction or recovery set out in Articles 43 and 44.

42.3 Effects

If the *Commission* rejects costs at the time of an **interim payment** or **the payment of the balance**, it will deduct them from the total eligible costs declared, for the action, in the periodic or final summary financial statement (see Articles 20.3 and 20.4). It will then calculate the interim payment or payment of the balance as set out in Articles 21.3 or 21.4.

If the *Commission* — **after an interim payment but before the payment of the balance** — rejects costs declared in a periodic summary financial statement, it will deduct them from the total eligible costs declared, for the action, in the next periodic summary financial statement or in the final summary financial statement. It will then calculate the interim payment or payment of the balance as set out in Articles 21.3 or 21.4.

If the *Commission* rejects costs **after the payment of the balance**, it will deduct the amount rejected from the total eligible costs declared, by the beneficiary, in the final summary financial statement. It will then calculate the revised final grant amount as set out in Article 5.4.

ARTICLE 43 — REDUCTION OF THE GRANT

43.1 Conditions

43.1.1 The *Commission* may — **at the payment of the balance** or **afterwards** — reduce the maximum grant amount (see Article 5.1), if the action has not been implemented properly as described in Annex 1 or another obligation under the Agreement has been breached.

43.1.2 The *Commission* may also reduce the maximum grant amount on the basis of the **extension of findings from other grants to this grant**, under the conditions set out in Article 22.5.2.

43.2 Amount to be reduced — Calculation — Procedure

The amount of the reduction will be proportionate to the improper implementation of the action or to the seriousness of the breach.

Before reduction of the grant, the *Commission* will formally notify a '**pre-information letter**' to the coordinator or beneficiary concerned:

- informing it of its intention to reduce the grant, the amount it intends to reduce and the reasons why and

- inviting it to submit observations within 30 days of receiving notification

If the *Commission* does not receive any observations or decides to pursue reduction despite the observations it has received, it will formally notify **confirmation** of the reduction (if applicable, together with the notification of amounts due; see Article 21).

43.3 Effects

If the *Commission* reduces the grant at the time of **the payment of the balance**, it will calculate the reduced grant amount for the action and then determine the amount due as payment of the balance (see Articles 5.3.4 and 21.4).

If the *Commission* reduces the grant **after the payment of the balance**, it will calculate the revised final grant amount for the beneficiary concerned (see Article 5.4). If the revised final grant amount for the beneficiary concerned is lower than its share of the final grant amount, the *Commission* will recover the difference (see Article 44).

ARTICLE 44 — RECOVERY OF UNDUE AMOUNTS

44.1 Amount to be recovered — Calculation — Procedure

The *Commission* will — after **termination of the participation of a beneficiary, at the payment of the balance** or **afterwards** — claim back any amount that was paid but is not due under the Agreement.

Each beneficiary's financial responsibility in case of recovery is limited to its own debt, except for the amount retained for the Guarantee Fund (see Article 21.4).

44.1.1 Recovery after termination of a beneficiary's participation

If recovery takes place after termination of a beneficiary's participation (including the coordinator), the *Commission* will claim back the undue amount from the beneficiary concerned, by formally notifying it a debit note (see Article 50.2 and 50.3). This note will specify the amount to be recovered, the terms and the date for payment.

If payment is not made by the date specified in the debit note, the Commission will **recover** the amount:

(a) by '**offsetting**' it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the *Commission* may offset before the payment date specified in the debit note;

(b) *not applicable;*

(c) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial regulation No 966/2012.

If payment is not made by the date specified in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC[27] applies.

44.1.2 Recovery at payment of the balance

If the payment of the balance takes the form of a recovery (see Article 21.4), the *Commission* will formally notify a '**pre-information letter**' to the coordinator:

- informing it of its intention to recover, the amount due as the balance and the reasons why;
- specifying that it intends to deduct the amount to be recovered from the amount retained for the Guarantee Fund;
- requesting the coordinator to submit a report on the distribution of payments to the beneficiaries within 30 days of receiving notification, and
- inviting the coordinator to submit observations within 30 days of receiving notification.

If no observations are submitted or the *Commission* decides to pursue recovery despite the observations it has received, it will **confirm recovery** (together with the notification of amounts due; see Article 21.5) and:

- pay the difference between the amount to be recovered and the amount retained for the Guarantee Fund, **if the difference is positive** or
- formally notify to the coordinator a **debit note** for the difference between the amount to be recovered and the amount retained for the Guarantee Fund, **if the difference is negative**. This note will also specify the terms and the date for payment.

If the coordinator does not repay the *Commission* by the date in the debit note and has not submitted the report on the distribution of payments: the Commission will **recover** the amount set out in the debit note from the coordinator (see below).

If the coordinator does not repay the *Commission* by the date in the debit note, but has submitted the report on the distribution of payments: the *Commission* will:

(a) identify the beneficiaries for which the amount calculated as follows is negative:

{{{{beneficiary's costs declared in the final summary financial statement and approved by the *Commission* multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned}

divided by

the EU contribution for the action calculated according to Article 5.3.1}

[27] Directive 2007/64/EC of the European Parliament and of the Council of 13 November 2007 on payment services in the internal market amending Directives 97/7/EC, 2002/65/EC, 2005/60/EC and 2006/48/EC and repealing Directive 97/5/EC (OJ L 319, 05.12.2007, p. 1).

multiplied by

the final grant amount (see Article 5.3)},

minus

{pre-financing and interim payments received by the beneficiary}}.

(b) formally notify to each beneficiary identified according to point (a) a **debit note** specifying the terms and date for payment. The amount of the debit note is calculated as follows:

{{amount calculated according to point (a) for the beneficiary concerned

divided by

the sum of the amounts calculated according to point (a) for all the beneficiaries identified according to point (a)}

multiplied by

the amount set out in the debit note formally notified to the coordinator}.

If payment is not made by the date specified in the debit note, the *Commission* will **recover** the amount:

(a) by '**offsetting**' it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the *Commission* may offset before the payment date specified in the debit note;

(b) by **drawing on the Guarantee Fund**. The Commission will formally notify the beneficiary concerned the debit note on behalf of the Guarantee Fund and recover the amount:

(i) *not applicable;*

(ii) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

44.1.3 Recovery of amounts after payment of the balance

If, for a beneficiary, the revised final grant amount (see Article 5.4) is lower than its share of the final grant amount, it must repay the difference to the *Commission*.

The beneficiary's share of the final grant amount is calculated as follows:

{{{beneficiary's costs declared in the final summary financial statement and approved by the *Commission* multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned}

divided by

the EU contribution for the action calculated according to Article 5.3.1}

multiplied by

the final grant amount (see Article 5.3)}.

If the coordinator has not distributed amounts received (see Article 21.7), the *Commission* will also recover these amounts.

The *Commission* will formally notify a **pre-information letter** to the beneficiary concerned:

- informing it of its intention to recover, the due amount and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If no observations are submitted or the *Commission* decides to pursue recovery despite the observations it has received, it will **confirm** the amount to be recovered and formally notify to the beneficiary concerned a **debit note**. This note will also specify the terms and the date for payment.

If payment is not made by the date specified in the debit note, the *Commission* will **recover** the amount:

(a) by '**offsetting**' it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the *Commission* may offset before the payment date specified in the debit note;

(b) by **drawing on the Guarantee Fund**. The Commission will formally notify the beneficiary concerned the debit note on behalf of the Guarantee Fund and recover the amount:

(i) *not applicable;*

(ii) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the

date for payment in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

ARTICLE 45 — ADMINISTRATIVE AND FINANCIAL PENALTIES

45.1 Conditions

Under Articles 109 and 131(4) of the Financial Regulation No 966/2012, the *Commission* may impose **administrative** and **financial penalties** if a beneficiary:

(a) has committed substantial errors, irregularities or fraud or is in serious breach of its obligations under the Agreement or

(b) has made false declarations about information required under the Agreement or for the submission of the proposal (or has not supplied such information).

Each beneficiary is responsible for paying the financial penalties imposed on it.

Under Article 109(3) of the Financial Regulation No 966/2012, the Commission may — under certain conditions and limits — publish decisions imposing administrative or financial penalties.

45.2 Duration — Amount of penalty — Calculation

Administrative penalties exclude the beneficiary from all contracts and grants financed from the EU or Euratom budget for a maximum of five years from the date the infringement is established by the *Commission*.

If the beneficiary commits another infringement within five years of the date the first infringement is established, the *Commission* may extend the exclusion period up to 10 years.

Financial penalties will be between 2% and 10% of the maximum EU contribution indicated, for the beneficiary concerned, in the estimated budget (see Annex 2).

If the beneficiary commits another infringement within five years of the date the first infringement is established, the *Commission* may increase the rate of financial penalties to between 4% and 20%.

45.3 Procedure

Before applying a penalty, the *Commission* will formally notify the beneficiary concerned:

- informing it of its intention to impose a penalty, its duration or amount and the reasons why and
- inviting it to submit observations within 30 days.

If the *Commission* does not receive any observations or decides to impose the penalty despite of observations it has received, it will formally notify **confirmation** of the penalty to the beneficiary

concerned and — in case of financial penalties — deduct the penalty from the payment of the balance or formally notify a **debit note**, specifying the amount to be recovered, the terms and the date for payment.

If payment is not made by the date specified in the debit note, the Commission may **recover** the amount:

(a) by '**offsetting**' it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the *Commission* may offset before the payment date specified in the debit note;

(b) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

SECTION 2 LIABILITY FOR DAMAGES

ARTICLE 46 — LIABILITY FOR DAMAGES

46.1 Liability of the *Commission*

The *Commission* cannot be held liable for any damage caused to the beneficiaries or to third parties as a consequence of implementing the Agreement, including for gross negligence.

The *Commission* cannot be held liable for any damage caused by any of the beneficiaries or third parties involved in the action, as a consequence of implementing the Agreement.

46.2 Liability of the beneficiaries

46.2.1 Conditions

Except in case of force majeure (see Article 51), the beneficiaries must compensate the *Commission* for any damage it sustains as a result of the implementation of the action or because the action was not implemented in full compliance with the Agreement.

Each beneficiary is responsible for paying the damages claimed from it.

46.2.2 Amount of damages - Calculation

The amount the *Commission* can claim from a beneficiary will correspond to the damage caused by that beneficiary.

46.2.3 Procedure

Before claiming damages, the *Commission* will formally notify the beneficiary concerned:

- informing it of its intention to claim damages, the amount and the reasons why and
- inviting it to submit observations within 30 days.

If the *Commission* does not receive any observations or decides to claim damages despite the observations it has received, it will formally notify **confirmation** of the claim for damages and a **debit note**, specifying the amount to be recovered, the terms and the date for payment.

If payment is not made by the date specified in the debit note, the Commission may **recover** the amount:

(a) by '**offsetting**' it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Commission or an executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the *Commission* may offset before the payment date specified in the debit note;

(b) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

SECTION 3 SUSPENSION AND TERMINATION

ARTICLE 47 — SUSPENSION OF PAYMENT DEADLINE

47.1 Conditions

The *Commission* may — at any moment — suspend the payment deadline (see Article 21.2 to 21.4) if a request for payment (see Article 20) cannot be approved because:

(a) it does not comply with the provisions of the Agreement (see Article 20);

(b) the technical reports or financial reports have not been submitted or are not complete or additional information is needed, or

(c) there is doubt about the eligibility of the costs declared in the financial statements and additional checks, reviews, audits or investigations are necessary.

47.2 Procedure

The *Commission* will formally notify the coordinator of the suspension and the reasons why.

The suspension will **take effect** the day notification is sent by the *Commission* (see Article 52).

If the conditions for suspending the payment deadline are no longer met, the suspension will be **lifted** — and the remaining period will resume.

If the suspension exceeds two months, the coordinator may request the *Commission* if the suspension will continue.

If the payment deadline has been suspended due to the non-compliance of the technical or financial reports (see Article 20) and the revised report or statement is not submitted or was submitted but is also rejected, the *Commission* may also terminate the Agreement or the participation of the beneficiary (see Article 50.3.1(l)).

ARTICLE 48 — SUSPENSION OF PAYMENTS

48.1 Conditions

The *Commission* may — at any moment — suspend, in whole or in part, the pre-financing payment and interim payments for one or more beneficiaries or the payment of the balance for all beneficiaries, if a beneficiary:

(a) has committed or is suspected of having committed substantial errors, irregularities, fraud or serious breach of obligations in the award procedure or under this Agreement or

(b) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (**extension of findings from other grants to this grant**; see Article 22.5.2).

48.2 Procedure

Before suspending payments, the *Commission* will formally notify the coordinator:

- informing it of its intention to suspend payments and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the *Commission* does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify **confirmation** of the suspension. Otherwise, it will formally notify that the suspension procedure is not continued.

The suspension will **take effect** the day the confirmation notification is sent by the *Commission*.

If the conditions for resuming payments are met, the suspension will be **lifted**. The *Commission* will formally notify the coordinator.

During the suspension, the periodic report(s) (see Article 20.3) must not contain any individual financial statements from the beneficiary concerned. When the *Commission* resumes payments, the coordinator may include them in the next periodic report.

The beneficiaries may suspend implementation of the action (see Article 49.1) or terminate the Agreement or the participation of the beneficiary concerned (see Article 50.1 and 50.2).

ARTICLE 49 — SUSPENSION OF THE ACTION IMPLEMENTATION

49.1 Suspension of the action implementation, by the beneficiaries

49.1.1 Conditions

The beneficiaries may suspend implementation of the action or any part of it, if exceptional circumstances — in particular *force majeure* (see Article 51) — make implementation impossible or excessively difficult.

49.1.2 Procedure

The coordinator must immediately formally notify to the *Commission* the suspension (see Article 52), stating:

- the reasons why and
- the expected date of resumption.

The suspension will **take effect** the day this notification is received by the *Commission*.

Once circumstances allow for implementation to resume, the coordinator must immediately formally notify the *Commission* and request an **amendment** of the Agreement to set the date on which the action will be resumed, extend the duration of the action and make other changes necessary to adapt the action to the new situation (see Article 55) — unless the Agreement or the participation of a beneficiary has been terminated (see Article 50).

The suspension will be **lifted** with effect from the resumption date set out in the amendment. This date may be before the date on which the amendment enters into force.

Costs incurred during suspension of the action implementation are not eligible (see Article 6).

49.2 Suspension of the action implementation, by the *Commission*

49.2.1 Conditions

The *Commission* may suspend implementation of the action or any part of it:

(a) if a beneficiary has committed or is suspected of having committed substantial errors, irregularities, fraud or serious breach of obligations in the award procedure or under this Agreement;

(b) if a beneficiary has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (**extension of findings from other grants to this grant**; see Article 22.5.2), or

(c) if the action is suspected of having lost its scientific or technological relevance.

49.2.2 Procedure

Before suspending implementation of the action, the *Commission* will formally notify the coordinator:

- informing it of its intention to suspend the implementation and the reasons why and

- inviting it to submit observations within 30 days of receiving notification.

If the *Commission* does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify **confirmation** of the suspension. Otherwise, it will formally notify that the procedure is not continued.

The suspension will **take effect** five days after confirmation notification is received by the coordinator (or on a later date specified in the notification).

It will be **lifted** if the conditions for resuming implementation of the action are met.

The coordinator will be formally notified of the lifting and the Agreement will be **amended** to set the date on which the action will be resumed, extend the duration of the action and make other changes necessary to adapt the action to the new situation (see Article 55) — unless the Agreement has already been terminated (see Article 50).

The suspension will be lifted with effect from the resumption date set out in the amendment. This date may be before the date on which the amendment enters into force.

Costs incurred during suspension are not eligible (see Article 6).

The beneficiaries may not claim damages due to suspension by the *Commission* (see Article 46).

Suspension of the action implementation does not affect the *Commission's* right to terminate the Agreement or participation of a beneficiary (see Article 50), reduce the grant or recover amounts unduly paid (see Articles 43 and 44).

ARTICLE 50 — TERMINATION OF THE AGREEMENT OR OF THE PARTICIPATION OF ONE OR MORE BENEFICIARIES

50.1 Termination of the Agreement by the beneficiaries

50.1.1 Conditions and procedure

The beneficiaries may terminate the Agreement.

The coordinator must formally notify termination to the *Commission* (see Article 52), stating:

- the reasons why and

- the date the termination will take effect. This date must be after the notification.

If no reasons are given or if the *Commission* considers the reasons do not justify termination, the Agreement will be considered to have been '**terminated improperly**'.

The termination will **take effect** on the day specified in the notification.

50.1.2 Effects

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a periodic report (for the open reporting period until termination; see Article 20.3) and

(ii) the final report (see Article 20.4).

If the *Commission* does not receive the reports within the deadline (see above), only costs which are included in an approved periodic report will be taken into account.

The *Commission* will **calculate** the final grant amount (see Article 5.3) and the balance (see Article 21.4) on the basis of the reports submitted. Only costs incurred until termination are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

Improper termination may lead to a reduction of the grant (see Article 43).

After termination, the beneficiaries' obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38 and 40) continue to apply.

50.2 Termination of the participation of one or more beneficiaries, by the beneficiaries

50.2.1 Conditions and procedure

The participation of one or more beneficiaries may be terminated by the coordinator, on request of the beneficiary concerned or on behalf of the other beneficiaries.

The coordinator must formally notify termination to the *Commission* (see Article 52) and inform the beneficiary concerned.

If the coordinator's participation is terminated without its agreement, the formal notification must be done by another beneficiary (acting on behalf of the other beneficiaries).

The notification must include:

- the reasons why;

- the opinion of the beneficiary concerned (or proof that this opinion has been requested in writing);

- the date the termination takes effect. This date must be after the notification, and

- a request for amendment (see Article 55), with a proposal for reallocation of the tasks and the estimated budget of the beneficiary concerned (see Annexes 1 and 2) and, if necessary, the addition of one or more new beneficiaries (see Article 56). If termination takes effect after the period set out in Article 3, no request for amendment must be included unless the beneficiary concerned is the coordinator. In this case, the request for amendment must propose a new coordinator.

If this information is not given or if the *Commission* considers that the reasons do not justify termination, the participation will be considered to have been **terminated improperly**.

The termination will **take effect** on the day specified in the notification.

50.2.2 Effects

The coordinator must — within 30 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the beneficiary concerned and

(ii) if termination takes effect during the period set out in Article 3, a '**termination report**' from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Articles 20.3 and 20.4).

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 20.3).

If the request for amendment is rejected by the *Commission*, (because it calls into question the decision awarding the grant or breaches the principle of equal treatment of applicants), the Agreement may be terminated according to Article 50.3.1(c).

If the request for amendment is accepted by the *Commission*, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The *Commission* will **calculate** — on the basis of the periodic reports, the termination report and the report on the distribution of payments — if the (pre-financing and interim) payments received by the beneficiary concerned exceed the beneficiary's EU contribution (calculated by applying the reimbursement rate(s) to the eligible costs declared by the beneficiary and approved by the *Commission*). Only costs incurred by the beneficiary concerned until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

- If the payments received **exceed the amounts due**:

  - if termination takes effect during the period set out in Article 3 and the request for amendment is accepted, the beneficiary concerned must repay to the coordinator the amount unduly received. The *Commission* will formally notify the amount unduly received and request the beneficiary concerned to repay it to the coordinator within 30 days of receiving notification. If it does not repay the coordinator, the *Commission* will draw upon the Guarantee Fund to pay the coordinator and then notify a **debit note** on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- in all other cases (in particular if termination takes effect after the period set out in Article 3), the *Commission* will formally notify a **debit note** to the beneficiary concerned. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the *Commission* the amount due and the *Commission* will notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- if the beneficiary concerned is the former coordinator, it must repay the new coordinator according to the procedure above, unless:

  - termination is after an interim payment and

  - the former coordinator has not distributed amounts received as pre-financing or interim payments (see Article 21.7).

  In this case, the *Commission* will formally notify a **debit note** to the former coordinator. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the *Commission* the amount due. The *Commission* will then pay the new coordinator and notify a debit note on behalf of the Guarantee Fund to the former coordinator (see Article 44).

• If the payments received **do not exceed the amounts due**: amounts owed to the beneficiary concerned will be included in the next interim or final payment.

If the *Commission* does not receive the termination report within the deadline (see above), only costs included in an approved periodic report will be taken into account.

If the *Commission* does not receive the report on the distribution of payments within the deadline (see above), it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned and that

- the beneficiary concerned must not repay any amount to the coordinator.

Improper termination may lead to a reduction of the grant (see Article 43) or termination of the Agreement (see Article 50).

After termination, the concerned beneficiary's obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38 and 40) continue to apply.

50.3 Termination of the Agreement or the participation of one or more beneficiaries, by the *Commission*

50.3.1 Conditions

The *Commission* may terminate the Agreement or the participation of one or more beneficiaries, if:

(a) one or more beneficiaries do not accede to the Agreement (see Article 56);

(b) a change to their legal, financial, technical, organisational or ownership situation is likely to substantially affect or delay the implementation of the action or calls into question the decision to award the grant;

(c) following termination of participation for one or more beneficiaries (see above), the necessary changes to the Agreement would call into question the decision awarding the grant or breach the principle of equal treatment of applicants (see Article 55);

(d) implementation of the action is prevented by force majeure (see Article 51) or suspended by the coordinator (see Article 49.1) and either:

(i) resumption is impossible, or

(ii) the necessary changes to the Agreement would call into question the decision awarding the grant or breach the principle of equal treatment of applicants;

(e) a beneficiary is declared bankrupt, being wound up, having its affairs administered by the courts, has entered into an arrangement with creditors, has suspended business activities, or is subject to any other similar proceedings or procedures under national law;

(f) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has been found guilty of professional misconduct, proven by any means;

(g) a beneficiary does not comply with the applicable national law on taxes and social security;

(h) the action has lost scientific or technological relevance;

(i) *not applicable;*

(j) *not applicable;*

(k) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed fraud, corruption, or is involved in a criminal organisation, money laundering or any other illegal activity affecting the EU's financial interests;

(l) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has — in the award procedure or under the Agreement — committed:

(i) substantial errors, irregularities, fraud or

(ii) serious breach of obligations, including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles;

(m) a beneficiary has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant ('**extension of findings from other grants to this grant**').

50.3.2 Procedure

Before terminating the Agreement or participation of one or more beneficiaries, the *Commission* will formally notify the coordinator:

- informing it of its intention to terminate and the reasons why and

- inviting it, within 30 days of receiving notification, to submit observations and — in case of Point (l.ii) above — to inform the *Commission* of the measures to ensure compliance with the obligations under the Agreement.

If the *Commission* does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify to the coordinator **confirmation** of the termination and the date it will take effect. Otherwise, it will formally notify that the procedure is not continued.

The termination will **take effect**:

- for terminations under Points (b), (c), (e), (g), (h), (j), and (l.ii) above: on the day specified in the notification of the confirmation (see above);

- for terminations under Points (a), (d), (f), (i), (k), (l.i) and (m) above: on the day after the notification of the confirmation is received by the coordinator.

50.3.3 Effects

(a) for **termination of the Agreement**:

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a periodic report (for the last open reporting period until termination; see Article 20.3) and

(ii) a final report (see Article 20.4).

If the Agreement is terminated for breach of the obligation to submit the reports (see Articles 20.8 and 50.3.1(l)), the coordinator may not submit any reports after termination.

If the *Commission* does not receive the reports within the deadline (see above), only costs which are included in an approved periodic report will be taken into account.

The *Commission* will **calculate** the final grant amount (see Article 5.3) and the balance (see Article 21.4) on the basis of the reports submitted. Only costs incurred until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

This does not affect the *Commission's* right to reduce the grant (see Article 43) or to impose administrative and financial penalties (Article 45).

The beneficiaries may not claim damages due to termination by the *Commission* (see Article 46).

After termination, the beneficiaries' obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38 and 40) continue to apply.

(b) for **termination of the participation of one or more beneficiaries**:

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the beneficiary concerned;

(ii) a request for amendment (see Article 55), with a proposal for reallocation of the tasks and estimated budget of the beneficiary concerned (see Annexes 1 and 2) and, if necessary, the addition of one or more new beneficiaries (see Article 56). If termination is notified after the period set out in Article 3, no request for amendment must be submitted unless the beneficiary concerned is the coordinator. In this case the request for amendment must propose a new coordinator, and

(iii) if termination takes effect during the period set out in Article 3, a **termination report** from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Article 20).

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 20.3).

If the request for amendment is rejected by the *Commission* (because it calls into question the decision awarding the grant or breaches the principle of equal treatment of applicants), the Agreement may be terminated according to Article 50.3.1(c).

If the request for amendment is accepted by the *Commission*, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The *Commission* will **calculate** — on the basis of the periodic reports, the termination report and the report on the distribution of payments — if the (pre-financing and interim) payments received by the beneficiary concerned exceed the beneficiary's EU contribution (calculated by applying the reimbursement rate(s) to the eligible costs declared by the beneficiary and approved by the *Commission*). Only costs incurred by the beneficiary concerned until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

- If the payments received **exceed the amounts due**:

  - if termination takes effect during the period set out in Article 3 and the request for amendment is accepted, the beneficiary concerned must repay to the coordinator the amount unduly received. The *Commission* will formally notify the amount unduly received and request the beneficiary concerned to repay it to the coordinator within 30 days of receiving notification. If it does not repay the coordinator, the *Commission* will draw upon the Guarantee Fund to pay the coordinator and then notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

  - in all other cases, in particular if termination takes effect after the period set out in Article 3, the *Commission* will formally notify a **debit note** to the beneficiary concerned. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the *Commission* the amount due and the *Commission* will notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- if the beneficiary concerned is the former coordinator, it must repay the new coordinator the amount unduly received, unless:

  - termination takes effect after an interim payment and

  - the former coordinator has not distributed amounts received as pre-financing or interim payments (see Article 21.7)

  In this case, the *Commission* will formally notify a **debit note** to the former coordinator. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the *Commission* the amount due. The *Commission* will then pay the new coordinator and notify a debit note on behalf of the Guarantee Fund to the former coordinator (see Article 44).

• If the payments received **do not exceed the amounts due**: amounts owed to the beneficiary concerned will be included in the next interim or final payment.

If the *Commission* does not receive the termination report within the deadline (see above), only costs included in an approved periodic report will be taken into account.

If the *Commission* does not receive the report on the distribution of payments within the deadline (see above), it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned, and that

- the beneficiary concerned must not repay any amount to the coordinator.

After termination, the concerned beneficiary's obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38 and 40) continue to apply.

SECTION 4 FORCE MAJEURE

ARTICLE 51 — FORCE MAJEURE

'Force majeure' means any situation or event that:

- prevents either party from fulfilling their obligations under the Agreement,

- was unforeseeable, exceptional situation and beyond the parties' control,

- was not due to error or negligence on their part (or on the part of third parties involved in the action), and

- proves to be inevitable in spite of exercising all due diligence.

The following cannot be invoked as force majeure:

- any default of a service, defect in equipment or material or delays in making them available, unless they stem directly from a relevant case of force majeure,

- labour disputes or strikes, or

- financial difficulties.

Any situation constituting force majeure must be formally notified to the other party without delay, stating the nature, likely duration and foreseeable effects.

The parties must immediately take all the necessary steps to limit any damage due to force majeure and do their best to resume implementation of the action as soon as possible.

The party prevented by force majeure from fulfilling its obligations under the Agreement cannot be considered in breach of them.

CHAPTER 7 FINAL PROVISIONS

ARTICLE 52 — COMMUNICATION BETWEEN THE PARTIES

52.1 Form and means of communication

Communication under the Agreement (information, requests, submissions, 'formal notifications', etc.) must:

- be made in writing and

- bear the number of the Agreement.

Until the payment of the balance: all communication must be made through the electronic exchange system and using the forms and templates provided there.

After the payment of the balance: formal notifications must be made by registered post with proof of delivery ('formal notification on paper').

Communications in the electronic exchange system must be made by persons authorised according to the 'Terms and Conditions of Use of the electronic exchange system'. For naming the authorised persons, each beneficiary must have designated — before the signature of this Agreement — a 'Legal Entity Appointed Representative (LEAR)'. The role and tasks of the LEAR are stipulated in his/her appointment letter (see Terms and Conditions of Use of the electronic exchange system).

If the electronic exchange system is temporarily unavailable, instructions will be given on the Commission websites.

52.2 Date of communication

Communications are considered to have been made when they are sent by the sending party (i.e. on the date and time they are sent through the electronic exchange system).

Formal notifications through the **electronic** exchange system are considered to have been made when they are received by the receiving party (i.e. on the date and time of acceptance by the receiving party, as indicated by the time stamp). A formal notification that has not been accepted within 10 days after sending is considered to have been accepted.

Formal notifications **on paper** sent by **registered post** with proof of delivery (only after the payment of the balance) are considered to have been made on either:

- the delivery date registered by the postal service or
- the deadline for collection at the post office.

If the electronic exchange system is temporarily unavailable, the sending party cannot be considered in breach of its obligation to send a communication within a specified deadline.

52.3 Addresses for communication

The **electronic** exchange system must be accessed via the following URL:

https://ec.europa.eu/research/participants/portal/desktop/en/projects/

The *Commission* will formally notify the coordinator and beneficiaries in advance any changes to this URL.

Formal notifications on paper (only after the payment of the balance) addressed **to the *Commission*** must be sent to the following address:

European Commission
Directorate General for Communications Networks, Content and Technology
Health and Well-being
BU25 03/090
B-1049 Brussels Belgium

Formal notifications on paper (only after the payment of the balance) addressed **to the beneficiaries** must be sent to their legal address as specified in the 'Beneficiary Register'.

ARTICLE 53 — INTERPRETATION OF THE AGREEMENT

53.1 Precedence of the Terms and Conditions over the Annexes

The provisions in the Terms and Conditions of the Agreement take precedence over its Annexes.

Annex 2 takes precedence over Annex 1.

53.2 Privileges and immunities

Not applicable

ARTICLE 54 — CALCULATION OF PERIODS, DATES AND DEADLINES

In accordance with Regulation No 1182/71[28], periods expressed in days, months or years are calculated from the moment the triggering event occurs.

The day during which that event occurs is not considered as falling within the period.

[28] Regulation (EEC, Euratom) No 1182/71 of the Council of 3 June 1971 determining the rules applicable to periods, dates and time-limits (OJ L 124, 8.6.1971, p. 1).

ARTICLE 55 — AMENDMENTS TO THE AGREEMENT

55.1 Conditions

The Agreement may be amended, unless the amendment entails changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

Amendments may be requested by any of the parties.

55.2 Procedure

The party requesting an amendment must submit a request for amendment signed in the electronic exchange system (see Article 52).

The coordinator submits and receives requests for amendment on behalf of the beneficiaries (see Annex 3).

If a change of coordinator is requested without its agreement, the submission must be done by another beneficiary (acting on behalf of the other beneficiaries).

The request for amendment must include:

- the reasons why;
- the appropriate supporting documents;
- for a change of coordinator without its agreement: the opinion of the coordinator (or proof that this opinion has been requested in writing).

The *Commission* may request additional information.

If the party receiving the request agrees, it must sign the amendment in the electronic exchange system within 45 days of receiving notification (or any additional information the *Commission* has requested). If it does not agree, it must formally notify its disagreement within the same deadline. The deadline may be extended, if necessary for the assessment of the request. If no notification is received within the deadline, the request is considered to have been rejected

An amendment **enters into force** on the day of the signature of the receiving party.

An amendment **takes effect** on the date agreed by the parties or, in the absence of such an agreement, on the date on which the amendment enters into force.

ARTICLE 56 — ACCESSION TO THE AGREEMENT

56.1 Accession of the beneficiaries mentioned in the Preamble

The other beneficiaries must accede to the Agreement by signing the Accession Form (see Annex 3) in the electronic exchange system (see Article 52) within 30 days after its entry into force (see Article 58).

They will assume the rights and obligations under the Agreement with effect from the date of its entry into force (see Article 58).

If a beneficiary does not accede to the Agreement within the above deadline, the coordinator must — within 30 days — request an amendment to make any changes necessary to ensure proper implementation of the action. This does not affect the *Commission's* right to terminate the Agreement (see Article 50).

56.2 Addition of new beneficiaries

In justified cases, the beneficiaries may request the addition of a new beneficiary.

For this purpose, the coordinator must submit a request for amendment in accordance with Article 55. It must include an Accession Form (see Annex 3) signed by the new beneficiary in the electronic exchange system (see Article 52).

New beneficiaries must assume the rights and obligations under the Agreement with effect from the date of their accession specified in the Accession Form (see Annex 3).

ARTICLE 57 — APPLICABLE LAW AND SETTLEMENT OF DISPUTES

57.1 Applicable law

The Agreement is governed by the applicable EU law, supplemented if necessary by the law of Belgium.

57.2 Dispute settlement

If a dispute concerning the interpretation, application or validity of the Agreement cannot be settled amicably, the General Court — or, on appeal, the Court of Justice of the European Union — has sole jurisdiction. Such actions must be brought under Article 272 of the Treaty on the Functioning of the EU (TFEU).

If a dispute concerns administrative or financial penalties, offsetting or an enforceable decision under Article 299 TFEU (see Articles 44, 45 and 46), the beneficiaries must bring action before the General Court — or, on appeal, the Court of Justice of the European Union — under Article 263 TFEU.

ARTICLE 58 — ENTRY INTO FORCE OF THE AGREEMENT

The Agreement will enter into force on the day of signature by the *Commission* or the coordinator, depending on which is later.

SIGNATURES

For the coordinator

For the *Commission*

EUROPEAN COMMISSION

Directorate General for Communications Networks, Content and Technology

Health and Well-being

ANNEX 1 (part A)

Research and Innovation action

NUMBER — 689617 — EurValve

Table of Contents

1.1. The project summary

Project Number [1]	689617	Project Acronym [2]	EurValve

One form per project

General information	
Project title [3]	Personalised Decision Support for Heart Valve Disease
Starting date [4]	01/02/2016
Duration in months [5]	36
Call (part) identifier [6]	H2020-PHC-2015-single-stage
Topic	PHC-30-2015 Digital representation of health data to improve disease diagnosis and treatment
Fixed EC Keywords	Artificial Intelligence & Decision support
Free keywords	in silico, valvular, heart,

Abstract [7]

Valvular Heart Disease currently affects 2.5% of the population, but is overwhelmingly a disease of the elderly and consequently on the rise. It is dominated by two conditions, Aortic Stenosis and Mitral Regurgitation, both of which are associated with significant morbidity and mortality, yet which pose a truly demanding challenge for treatment optimisation. By combining multiple complex modelling components developed in recent EC-funded research projects, a comprehensive, clinically-compliant decision-support system will be developed to meet this challenge, by quantifying individualised disease severity and patient impairment, predicting disease progression, ranking the effectiveness of alternative candidate procedures, and optimising the patient-specific intervention plan. This algorithmically-driven process will dramatically improve outcomes and consistency across Europe in this fast-growing patient group, maximising individual, societal and economic outcomes.

1.2. List of Beneficiaries

Project Number [1]	689617	Project Acronym [2]	EurValve

List of Beneficiaries

No	Name	Short name	Country	Project entry month[8]	Project exit month
1	THE UNIVERSITY OF SHEFFIELD	USFD	United Kingdom	1	36
2	ANSYS FRANCE SAS	ANSYS	France	1	36
3	Stichting Catharina Ziekenhuis	CATH	Netherlands	1	36
4	AKADEMIA GORNICZO-HUTNICZA IM. STANISLAWA STASZICA W KRAKOWIE	CYFRONET	Poland	1	36
5	DEUTSCHES HERZZENTRUM BERLIN	DHZB	Germany	1	36
6	UNIVERSITE DE RENNES I	UR1	France	1	36
7	MAX-DELBRUCK-CENTRUM FUR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT	MDC	Germany	1	36
8	PHILIPS ELECTRONICS NEDERLAND B.V.	PEN	Netherlands	1	36
9	Philips GmbH	PHILIPS	Germany	1	36
10	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST	STH	United Kingdom	1	36
11	THERENVA	THERENVA	France	1	36
12	TECHNISCHE UNIVERSITEIT EINDHOVEN	TU/e	Netherlands	1	36
13	UNIVERSITY OF BRISTOL	UBRIS	United Kingdom	1	36

1.3. Workplan Tables - Detailed implementation

1.3.1. WT1 List of work packages

WP Number [9]	WP Title	Lead beneficiary [10]	Person-months [11]	Start month [12]	End month [13]
WP1	Project Management	1 - USFD	40.00	1	36
WP2	Infrastructure	4 - CYFRONET	98.00	1	36
WP3	Software Components	9 - PHILIPS	107.00	1	36
WP4	DP Definition, Data Collection	5 - DHZB	89.00	1	36
WP5	Decision Support System	11 - THERENVA	96.00	1	36
WP6	DSS Operation	5 - DHZB	84.00	1	36
WP7	Exploitation	11 - THERENVA	38.00	1	36
		Total	552.00		

1.3.2. WT2 list of deliverables

Deliverable Number [14]	Deliverable Title	WP number [9]	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D1.1	Periodic Report #1	WP1	1 - USFD	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D1.2	Periodic Report #2	WP1	1 - USFD	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D1.3	Project Final Report	WP1	1 - USFD	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D2.1	Data Requirements	WP2	10 - STH	Report	Confidential, only for members of the consortium (including the Commission Services)	3
D2.2	Infrastructure Design Recommendations	WP2	4 - CYFRONET	Report	Public	4
D2.3	Data Workshop	WP2	5 - DHZB	Other	Public	8
D2.4	Infrastructure Beta Release	WP2	4 - CYFRONET	Other	Confidential, only for members of the consortium (including the Commission Services)	15
D2.5	Infrastructure Candidate Release	WP2	4 - CYFRONET	Other	Confidential, only for members of the consortium (including the Commission Services)	30
D3.1	Software Components Specifications	WP3	8 - PEN	Report	Public	4
D3.2	Software Components Beta Release	WP3	8 - PEN	Other	Confidential, only for members of the consortium (including the Commission Services)	15

Deliverable Number [14]	Deliverable Title	WP number [9]	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D3.3	ROM Tools Manual	WP3	2 - ANSYS	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.4	Software Components Candidate Release	WP3	8 - PEN	Other	Confidential, only for members of the consortium (including the Commission Services)	30
D4.1	Digital Patient Definition	WP4	5 - DHZB	Report	Public	3
D4.2	Clinical Cohort Specification	WP4	5 - DHZB	Report	Public	4
D4.3	Data Status Report	WP4	5 - DHZB	Report	Public	15
D4.4	Literature and Guidelines Report	WP4	8 - PEN	Report	Public	15
D4.5	Activity Monitoring Report	WP4	13 - UBRIS	Report	Confidential, only for members of the consortium (including the Commission Services)	15
D4.6	Activity Monitoring Data Analysis	WP4	13 - UBRIS	Report	Confidential, only for members of the consortium (including the Commission Services)	28
D4.7	Data Summary and Review	WP4	5 - DHZB	Report	Public	30
D5.1	Decision Support System Specification	WP5	11 - THERENVA	Report	Public	6
D5.2	Decision Support System Beta Release	WP5	11 - THERENVA	Other	Confidential, only for members of the consortium (including the Commission Services)	21
D5.3	Case-Based Reasoning Module	WP5	6 - UR1	Other	Confidential, only for members of the consortium (including the Commission Services)	21

Deliverable Number [14]	Deliverable Title	WP number [9]	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D5.4	Decision Support System Candidate Release	WP5	11 - THERENVA	Other	Confidential, only for members of the consortium (including the Commission Services)	32
D6.1	Model-based Data Augmentation Report	WP6	1 - USFD	Report	Public	28
D6.2	Model-based Learning Report	WP6	8 - PEN	Report	Public	28
D6.3	Final DSS Evaluation Report	WP6	5 - DHZB	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D6.4	Platform Evaluation Report	WP6	4 - CYFRONET	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D7.1	Exploitation Initial Report	WP7	11 - THERENVA	Report	Confidential, only for members of the consortium (including the Commission Services)	12
D7.2	Exploitation Interim Report	WP7	11 - THERENVA	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D7.3	Exploitation Final Report	WP7	11 - THERENVA	Report	Confidential, only for members of the consortium (including the Commission Services)	36

1.3.3. WT3 Work package descriptions

Work package number [9]	WP1	**Lead beneficiary** [10]	1 - USFD
Work package title	Project Management		
Start month	1	**End month**	36

Objectives

1. To ensure that the project is appropriately coordinated and managed according to the implementation plan, corrective actions being taken where necessary.
2. To establish a project management structure that ensures efficient operational control of administrative and financial tasks and project conduct in accordance with the Consortium Agreement.
3. To implement procedures, employ tools and marshal resources so as to assure contract fulfilment, with timely delivery of high-quality results.
4. To carry out routine reporting and administrative tasks, including progress updates to the Commission, financial distribution to partners and the preparation of project amendments as may be required.

Description of work and role of partners

WP1 - Project Management [Months: 1-36]
USFD, ANSYS, CATH, CYFRONET, DHZB , UR1, MDC, PEN, PHILIPS, STH , THERENVA, TU/e, UBRIS
Task 1.1 Scientific Project Coordination
Activity Leader: USFD. Contact person: Prof Rod Hose (USFD); d.r.hose@sheffield.ac.uk

Overall scientific co-ordination of the work packages and technical activities of the project, ensuring the project's intermediate and final results are produced on time and to high quality. Taking decisions regarding the overall policy and technical strategy of the project, including the approval of the work plan and financial plan for subsequent periods, high-level conflict resolution, knowledge management, IPR and ethical issues, participation of new partners, and ensuring promotion of gender equity. Coordination will be overseen by the project Coordinator and will involve the General Assembly (GA), the Project Board (PB) and Work Package Leaders (WPL), with support of the Project Management Office (PMO).

Task 1.2 Operational Management
Activity Leader: USFD. Contact person: Prof Rod Hose (USFD); d.r.hose@sheffield.ac.uk

Day-to-day management of the project. Follow-up of tasks and monitoring of the project work plan and time schedule. Administration of resources. Communication strategy implementation and resolution of conflicts among partners and consortium. Knowledge management. Consortium Agreement implementation. Meetings organisation and minutes production. Permanent contact point for the project and liaison with the EC's appointed Project Officer. Timely delivery of project's reports and deliverables and achievement of milestones. Production of administrative and financial periodic reports and audits. Implemented through the PMO giving support and assistance to the Coordinator, the PB, the GA and Consortium as a whole.

Task 1.3 Knowledge Management
Activity Leader: USFD. Contact person: Prof Rod Hose (USFD); d.r.hose@sheffield.ac.uk

To ensure appropriate and robust Knowledge Management of the project's results, ensuring output disseminate is controlled in accordance with the Consortium Agreement and the requirements of public and controlled-domain media including peer-reviewed journals.

Partner Roles:
USFD will chair the project management board and be responsible for all communications with the Commission. It will appoint a project manager to the task of managing this process.
All will take an active role in both the day to day and long term management of the project, and be responsible for their own budgets and the reporting of effort and expenditure against them.

Participation per Partner

Partner number and short name	WP1 effort
1 - USFD	17.00
2 - ANSYS	1.00
3 - CATH	2.00
4 - CYFRONET	2.00
5 - DHZB	2.00
6 - UR1	2.00
7 - MDC	2.00
8 - PEN	2.00
9 - PHILIPS	2.00
10 - STH	2.00
11 - THERENVA	2.00
12 - TU/e	2.00
13 - UBRIS	2.00
Total	40.00

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D1.1	Periodic Report #1	1 - USFD	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D1.2	Periodic Report #2	1 - USFD	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D1.3	Project Final Report	1 - USFD	Report	Confidential, only for members of the consortium (including the Commission Services)	36

Description of deliverables

D1.1 Periodic Report #1
D1.2 Periodic Report #2
D1.3 Final Report

D1.1 : Periodic Report #1 [18]

Periodic Report #1

D1.2 : Periodic Report #2 [36]
Periodic Report #2
D1.3 : Project Final Report [36]
Project Final Report

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification

Work package number [9]	WP2	Lead beneficiary [10]	4 - CYFRONET
Work package title	Infrastructure		
Start month	1	End month	36

Objectives

WP2 will elaborate and operate a flexible, easy to use environment for the development, deployment and execution of large scale simulations, required for learning process development and for sensitivity analyses (a 'Model Execution Environment'), and for the associated data storage. The simulations will produce decision rule-sets that will be transferred from the research infrastructure to the DSS, while built-in visualisation facilities will enable access to cloud services from the local workstation.
The simulations will be run on external federated compute and storage resources exploiting recent advances in distributed computing, especially in cloud and container technologies. Usage of resources will be optimised taking into account multiple factors including cost and execution time. WP2 will closely collaborate with WP3 in the optimisation of their software modules.

The specific objectives are:
1. To provide and to develop the necessary infrastructure to:
* Collect, represent, annotate and publish the core homogeneous data
* Store and give secure access to the participating clinical centres and to the development partners to the necessary data.
* Execute the models in the most appropriate computational environment (private workstation, private cloud, public cloud) according to need.
* Support real-time multiscale visualisation.

2. To develop an integrated security system supporting:
* Authentication and authorisation
* Data encryption for secure processing in public clouds.

3. To deploy and operate the developed infrastructure, ensuring:
* Quality of software components deployed and installed
* Quality of service, including such aspects as availability, responsiveness and cost efficiency

Description of work and role of partners

WP2 - Infrastructure [Months: 1-36]
CYFRONET, USFD, DHZB , UR1, STH
Task 2.1 Construction of Data Warehouse and Provision of Data Collection and Publication Suite: Activity Leader: STHFT. Contact person: Dr Steven Wood (STHFT); steven.wood@sth.nhs.uk

Data hosting facilities, data collection.
The data management infrastructure for EurValve encompasses data hosting and data collection.
Data hosting will use the technology stack developed as part of the VPH-Share project. This includes tools for extraction and transformation of clinical data from a wide variety of electronic systems and its hosting in a web based platform for access by the scientific researchers and their computational processes. These tools have been extensively tested on a large number of projects and since the partner STH was the lead developer we believe this will provide a reliable and extensible platform for researchers.
Data collection will employ Trial Connect, a purpose-built system commercially available from Deutsche Telekom and able to work cooperatively with external data repositories. STHFT will work with DHZB to:
o Set up the trial and eCRF environment
o Provide an introduction to all clinical partners
o Support end users
o Mediate further technical help and any project-specific adaptations with the developers.
o Include STH domain-specific tools as may be required

Task 2.2 Model Execution Environment
Activity Leader: CYFRONET. Contact person: Maciej Malawski malawski@agh.edu.pl

Execution environment, interface to data warehouse and to modelling tools. Private workstation, private and public clouds.

This task will develop a Model Execution Environment, supporting a wide range of models required for a DSS, such as CellML models and HPC applications including support for Ansys, Matlab and legacy services. The environment will leverage the Atmosphere platform developed in VPH-Share, to give access to the already deployed tools and services within the framework. However, in order to enable better flexibility and a wide range of deployment scenarios, we will employ the latest advances in cloud technologies, such as lightweight containers (e.g. Docker.io) and high-level public cloud services, e.g. as AWS Lambda or Microsoft Azure WebJobs. The environment will support generic architectures of DSS and distributed DSS, with data/model exchange between modules and multiple DSSs, in collaboration with WP3 and WP5. Support for high-throughput computing will be provided, with particular focus on sensitivity analysis studies with large parameter sets, by providing on-demand creation of a large pool of computing resources and their scalable management matched to need.
Based on the detailed analysis of requirements of models and deployment scenarios, together with the evaluation of current state of the art in rapidly changing cloud technologies performed in the initial phase of this ask, we will design a generic architecture of the platform and the interfaces it will provide to the components and the integrated DSS. It will be based on best practices in distributed systems design, and established standards, such as REST APIs. The prototype of the environment will be released quickly to the developers of selected components, to get feedback and identify the potential issues at the early stage. By using the testing methodology defined in WP6, the prototype will be incrementally improved by adding support for additional types of models and external cloud services.

Task 2.3 Integrated Security and Data Encryption
Activity Leader: CYFRONET (with STHFT) Contact person: Jan Meizner j.meizner@cyfronet.pl

Authentication, authorisation, data protection provided in collaboration with Task 2.1
This task will provide the solutions for the three main aspects of security. The first one is related to ensuring proper Authentication, Authorisation and Accounting mechanisms. The second one will provide high level of data security during storage and processing phases for services running in Cloud (especially public and hybrid one). Finally, an optional mechanism that ensures that data cannot be recovered using reasonable time and resources after being deleted will be also provided.
Our goal is to provide lightweight solution which would not impact performance of the services, yet on the other hand be pluggable and extendable to permit integration with various state-of-the-art security mechanisms, such as OAuth. We plan to design and develop mechanism that would combine suitable well-established cryptographic standards (including AES and SHA), with key distribution mechanisms, as well as data dispersal to different zones to ensure secure storage of data in the cloud. Also we will propose mechanism to move data in and out of the cloud for the purpose of computations in a safe (private) zone. Where appropriate we will base our work on best available solutions including software components as well as services offered by the IaaS providers such as AWS VPC and CloudHSM.
One of the crucial parts of our work will be to establish mechanism for risk assessment required to establish adequate security levels for given datasets. The categorisation of the confidential data needs to be done mainly based on the risk of identifying a given person. Highly personal (non-anonymised) data needs to be processed at hospital internal infrastructure only. Anonymised data with high probability of being de-anonymised (such as DICOM images) should be processed in restricted zone (e.g. partners private cloud). Finally non-critical and anonymised data (like statistical data) could be processed in the public cloud providing all security precautions are met.

Task 2.4 Real-time Multiscale Visualisation
Activity Leader: CYFRONET (with STHFT) Contact person: Daniel Harężlak dharezlak@gmail.com

Tools for real-time multiscale visualisation within a Web browser
In this task we will develop a set of tools enabling real-time visualisation of multi-scale simulation data. Developed utilities will support data transfer from computing nodes to user's client application where visualisation will take place using local hardware. For multiscale cases data streams coming from different simulation components, which can be distributed on computing resources, will be combined to present a coherent visual representation to the end user. Depending on the simulation code capabilities for changing runtime parameters a feedback loop from the visualisation client will be available (e.g. to transmit viewport information).
To ensure reliable, optimised data transfers and to start visualisation immediately relevant information is available, analysis of existing protocols and data representation schemes will be carried out with the main focus on web platforms (e.g. JSON, Web Sockets, Protocol Buffers). Final rendering of the visualised data will be performed on users' local resources with existing 3D libraries such as WebGL.
Integration with DSS, security and execution components will be subject to constant validation to ensure secure data transfers and good level of usability from the user's perspective.

Task 2.5 Platform quality assurance
Activity Leader: CYFRONET (with STHFT). Contact person: Piotr Nowakowski ymnowako@cyf-kr.edu.pl

Assuring quality of service of the platform, including availability, responsiveness and support
The quality and usability of software is a concern which must be specifically addressed if the project is to provide added value for medical practitioners, rather than simply constituting an exercise in software development. This is an issue which has fraught many collaborative undertakings and Consortium partners are well aware of the - somewhat contradictory - demands for software engineering flexibility and end-user satisfaction. Accordingly, a separate task is foreseen whose express responsibility will be to ensure that - regardless of any ongoing development/deployment work - project users retain access to a stable, coherent and usable platform. A dedicated production environment will be created, consisting of a separate pool of hardware resources, and the modules deployed therein will be subject to QA assessment. The task will also monitor quality indicators, including in particular platform uptime (as a percentage of the total time elapsed during the development phase of the project), and user QoE (quality of experience), which will be assessed by liaising with Valve-DSS user groups.
A monitoring infrastructure will be deployed in order to automatically detect any runtime problems and notify designated maintainers. Additionally, a helpdesk will be established, complete with electronic communication channels, enabling users to report problems and request assistance from platform developers whenever issues or questions arise.

Task 2.5 will also bear responsibility for ensuring that comprehensive and up-to-date online system documentation (including user manuals) is published.

Partner Roles:
CYFRONET will lead the work package and will develop the model execution environment, including taking responsibility for integration with the data warehouse, and will support WP5 in its deployment within WP5.
STHFT will design the data warehouse and the interface to the clinical systems.
DHZB will work with STHFT on the introduction and support of the clinical data system

Participation per Partner

Partner number and short name	WP2 effort
1 - USFD	5.00
4 - CYFRONET	47.00
5 - DHZB	21.00
6 - UR1	1.00
10 - STH	24.00
Total	98.00

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D2.1	Data Requirements	10 - STH	Report	Confidential, only for members of the consortium (including the Commission Services)	3
D2.2	Infrastructure Design Recommendations	4 - CYFRONET	Report	Public	4
D2.3	Data Workshop	5 - DHZB	Other	Public	8
D2.4	Infrastructure Beta Release	4 - CYFRONET	Other	Confidential, only for members of	15

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
				the consortium (including the Commission Services)	
D2.5	Infrastructure Candidate Release	4 - CYFRONET	Other	Confidential, only for members of the consortium (including the Commission Services)	30

Description of deliverables

D2.1 Requirements
D2.2 Analysis of technologies
D2.3 Deployment and training workshop
D2.4 Platform beta release
D2.5 Platform candidate release

D2.1 : Data Requirements [3]

Data warehouse and data publication suite requirements and functionality check

D2.2 : Infrastructure Design Recommendations [4]

Analysis of technologies for infrastructure: recommendations for design

D2.3 : Data Workshop [8]

Data management software deployment and training workshop and report

D2.4 : Infrastructure Beta Release [15]

Beta release of the infrastructure platform

D2.5 : Infrastructure Candidate Release [30]

Candidate release of the infrastructure platform

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS1	Specification phase complete	4 - CYFRONET	6	Specification phase complete
MS2	Data population commenced	5 - DHZB	9	Data warehouse population commenced at clinical centres
MS5	Candidate Release phase completed	11 - THERENVA	30	Candidate Release Phase completed
MS6	Final evaluation commenced	11 - THERENVA	33	Final Evaluation commenced

Work package number [9]	WP3	Lead beneficiary [10]	9 - PHILIPS
Work package title	Software Components		
Start month	1	End month	36

Objectives

This work package provides the software components that underpin the analysis processes. Objectives:

1. To provide and to develop the machine learning tools:
* To operate on literature data to infer missing data necessary for operation of the models and/or to extract rule sets (for example on interventional outcome) to interpret the model outputs.
* To operate on the project's own developing databases to infer missing data necessary for operation of the models and/or to extract rule sets (for example on interventional outcome) to interpret the model outputs.

2. To provide and to develop the models and software components:
* To yield detailed anatomical representations of an individual's mitral and aortic valve in different opening states together with the other required heart structures such as the left ventricle and the ascending aorta from CT and 3D TEE images or image sequences
* To extract quantitative measures based on the segmentation results, like aortic valve opening area, aortic or mitral annulus perimeter or mitral valve regurgitant area
* To facilitate subsequent blood flow simulations by providing suitable interfaces for the definition of boundary conditions and mesh models with sufficient resolution for subsequent volumetric meshing

3. To provide the underpinning compartmental (zero-d, lumped parameter) models that describe the distribution of flow, pressure, oxygen saturation and other physiological parameters in the cardiovascular circulation. These are important in their own right, but also provide boundary conditions for the localised anatomically accurate descriptions of the valve region, which are based on the segmentation of the medical images of the individual patient.

4. To provide and to develop the software components to support sensitivity studies and the derivation of confidence measures from multiple operations of the models.

Description of work and role of partners

WP3 - Software Components [Months: 1-36]
PHILIPS, USFD, ANSYS, UR1, MDC, PEN, TU/e
Task 3.1 Machine Learning Tools:
Activity Leader: PEN. Contact person: Dr Herman ter Horst (Philips); herman.ter.horst@philips.com

This task will develop and provide a machine learning module to infer data that is not available but is required for execution of computational, mechanistic, physiological models to provide information relevant for decision support. This task will also provide a module to access and to represent publication and population data and a module to develop rule sets from accumulated data.

As discussed in more detail above, this task will explore multiple machine learning paradigms in order to find the best possibilities for inferring data required for execution of models. This task involves, more specifically, selection and preparation of data for learning, development and selection of promising features for learning, development of machine learning algorithms, and derivation of indications of performance of these algorithms by using for example cross validation techniques.
The task has interfaces with T2.1 where the project's own data warehouse is developed, with T4.3, where publication and population data will be identified and uploaded to the system), with T4.1, where the application-specific patient avatar will be defined, and with T4.4, where relevant information from the literature is identified.

Task 3.2 Image Segmentation Tools
Activity Leader: PHILIPS. Contact person: Dr Juergen Weese (Philips); juergen.weese@philips.com

The models and software to yield detailed anatomical segmentations of the mitral and aortic valves from CT and 3D TEE images or image sequences together with segmentations of the left ventricle and the ascending aorta will be provided by this task. The work will build upon previously developed model-based segmentation technology that segments the heart and aortic and/or mitral valve by adapting a generic mesh model with trained boundary detectors to images. Unstructured meshes of the generic mesh model may be replaced by structured meshes to improve segmentation accuracy and provide

sufficient mesh quality for subsequent for 3D or 4D simulations from T3.4. In addition, information will be encoded into the generic models to facilitate setting up of simulations.

In particular, quantitative measures like aortic valve area, aortic or mitral annulus perimeter or mitral valve regurgitant area will be provided as input for the 0D Model from T3.3. The approaches will be trained on the cardiac CTA and 3D TEE data acquired within WP4 and improved to accurately capture the required anatomical details of the aortic and mitral valve as well as relevant surrounding structures. Details of the heart and valve anatomy may be captured by additional post-processing steps that are controlled by the model-based segmentation result. The segmentation algorithm will be validated quantitatively and made available together with manual correction tools to the consortium.

Task 3.3 Systems Models
Activity Leader: USFD. Contact person: Prof Rod Hose (USFD); d.r.hose@sheffield.ac.uk

The PHC-30 Call is clear that the expectation is to use existing computational models, not to develop them within the project. The focus of task 3.3 is to review the available physiological system models and to choose those most appropriate as central components of the Decision Support System. The first challenge is to balance the complexity of the models with the availability of patient data to tune the parameters in the model to represent the individual. The second challenge is to integrate the local three dimensional models of the valve with the lower order models that represent the rest of the system.

For the first challenge, there is a rich literature on cardiovascular systems models, reviewed in the state of the art section of this proposal. Of immense value is the set of curated models that are available through the CellML (https://www.cellml.org) model repository. There are currently over 50 models of the cardiovascular circulation in this freely-accessible repository, some of which have been contributed by the partners of the EurValve proposal. We propose to focus initially on one specific physiological model, contributed by the USFD group, based on an original publication by Shi and Korakianitis, which we judge to have the right balance of complexity and practicality for personalisation, but also to explore the comprehensive range of Guyton's models that are available in the same repository and which are particularly suited to the representation of cellular processes and of longer term physiological changes, including for example the effects of heart hypertrophy on pumping capability.
For the second challenge there are two approaches. One is to couple directly the multi-level models, with common or integral properties at the boundaries between them. USFD has strong experience of this approach in several cardiovascular applications. The second is to operate a 3D model to characterise the response over a range of operating conditions, to produce a lower order model that can be integrated directly with other lower-order models. This is the preferred approach for the current project, in which there is strong emphasis on the use of the model to extrapolate from measured states over the physiological envelope of the individual. Despite this strategy, there is still a requirement for extensive 3D computations and a need to conduct these as quickly and effectively as possible. This will be achieved using state-of-the-art advances in 3D modelling, as described in the next task.

Task 3.4 Variation and Sensitivity Analysis Tools
Activity Leader: TUE. Contact person: Prof Frans van de Vosse F.N.v.d.Vosse@tue.nl
Provision and deployment of software tools that perform variation and sensitivity analysis.

To assess the boundary conditions and model parameters that are most worthwhile to be measured patient-specifically and which ones can be based on population averages a variance-based sensitivity analysis will be applied. Sobol sensitivity indices[118] will be used to allocate each fraction of the total output uncertainty to corresponding input uncertainties, to a single model parameter, or to interactions between these parameters. These indices will be derived analytically from a meta-model, based upon generalized polynomial chaos expansions, that expands the model output space with multidimensional polynomials that dependent on the input parameters. These expansions will be obtained using least square regression[119]. A screening method of Morris[120] will be applied prior to the meta-model construction to reduce the dimensionality ingoing to a subset of important parameters. Input uncertainties will be based on measurement or population variations. For the 1D models this procedure is well defined and already successfully applied[121]. For 3D analysis The same procedure can be applied to the reduced order models applied in Task3.6 of this work package.

Also a step by step approach that starts with a reduced order model that will be expanded step-by-step with input that decreases output uncertainty of the prediction will be used. In that procedure the impact of reduced order modelling on the output parameter of interest can be investigated.

Also the difference of taking the boundary conditions for in- and outflow from directly assessed flow assessment and boundary conditions derived from 1D wave propagation or distributed 0D models for impact of valve disorders on the coronary circulation and myocardial contraction will investigated. Hereto, the physiological models of Task3.3 will be used as a point of departure.

The tools that will be used will be based on those developed in an earlier FP7 IP, VPH-Share but will be modified and extended in order to make the coupling with the physiological models of Task3.3, and the ROM in task 3.6. A link with the proteomics data analysis tool will be established via the system models.

Partner Responsibilities: TUE and USFD will implement the models whereas ANSYS will provide the non-linear dynamic reduced order versions of the models, USFD will provide the system models.

Task 3.5 Proteomics Data Analysis Tools
Activity Leader: MDC. Contact person: Prof Dr Martin Falcke martin.falcke@mdc-berlin.de

Samples will be obtained as pinch biopsies from the ventricular septum of 30 patients undergoing TAVI , and will be analysed by shotgun proteomics to a depth of about 3000. We will follow up on less abundant but functionally relevant proteins by selective reaction monitoring (SRM). The analysis will yield the abundance of proteins involved in excitation and contraction, relative to a reference sample.

Relative abundance of ion channel, pump and exchanger proteins will be used to personalise the ten-Tusscher model of membrane dynamics by scaling maximal conductances of ion channels, pumps and exchangers. On the basis of individual proteomics data the Rice model will be adapted to the normal human cardiomyocyte using the adaptation protocol described [Rice et. al. 2008], through adaptation of the transmission rates of the crossbridge cycle to match the normal human myosin heavy chain (MHC) V1 and V3 ratio using proteomics data from the reference human heart and using literature knowledge of hypertrophy associated MHC isoform switching122123. Normal endocardial [basal] Ca2+ transients from the literature [ref] will be used for fitting the reference model. The Rice et al., 2008 model parameters relating to collagen, titin, and troponin will be used for the reference heart. The individualised patient models will be developed using the proteomics data by adapting the model with the measured V1 and V3 MHC ratios, troponin levels, titin levels and collagen levels.

There are two potential difficulties in our approach. First, the myocardium contains endothelial cells, fibroblasts, myofibroblasts, neuronal cells, and vascular smooth muscle cells as well as myocytes. Thus although we expect the proteomics data to have a major contribution from cardiomyocytes, some of the measured proteins will be from other cell types. This difficulty will be mitigated to some extent because myocyte titin124, MHC125 and troponin126 have a different composition and so can be distinguished from proteins in vascular smooth muscle cells and myofibroblasts. Second, the link between protein abundance and function is not always simple. For example, ion channel function is modulated by intracellular signalling (for example B-adrenergic effects), and so the abundance of an ion channel protein may not reflect the actual maximal membrane conductance. Furthermore, many of the parameters in the force generation model do not have a direct physiological interpretation. However, our approach will be to determine if model personalisation based on changes in protein abundance alone can account for individual changes in cardiac performance, and this will allow us to determine whether it is necessary either to take into account ion channel modulation or to use a more detailed model both for contraction as well as intracellular signalling.

Task 3.6 Reduced Order Modelling Tools
Activity Leader: ANSYS. Contact person: Prof Michel Rochette Michel.Rochette@ansys.com

The EurValve project aims at combining parametric decomposition of the artery shape – in order to reduce the number of parameters required to describe the patient's anatomy – with ROM techniques to predict valves analysis and haemodynamics.

We consider the following subtasks
3.6.1. Parametric decomposition of the artery shape using population based modelling. From a database of patient arteries we extract the most important anatomical parameters.
3.6.2. ROM for parametric studies applied to a large set of anatomies described by the shape parameters. For each set of anatomical parameter values we store the transient solution vectors. Then we create the ROM database of off-line simulations (steady or transient). We could also consider valve disease parameters on that step.
3.6.3. Dynamic ROM (on-line). From the patient geometry and from the set of anatomical modes we compute the shape parameter values. From the ROM database we load the approximated transient haemodynamics solution corresponding to these shape parameters. Then using this transient solution and some velocity measurement given by MRI or echography we tune the boundary condition coefficient of Windkessel model. All evaluations of transient haemodynamics with respect to BC coefficient are performed using dynamic ROM.

Using our set of ROM techniques we could replace a full valve analysis which takes several days by an accurate evaluation of a few minutes. This quick valve analysis could be applied before and after intervention and will be a key component of valve DSS.

Partner Roles:

PHILIPS will lead the workpackage and provide the segmentation tools.
PEN will provide the machine learning tools
USFD will provide the existing models of systems physiology.
ANSYS, supported by USFD, will provide the Reduced Order Modelling tools that will underpin the solution of the complex valve flow dynamics in clinically-tractable timescales.
TUE with USFD will implement the tools for variation and sensitivity analysis.

Participation per Partner

Partner number and short name	WP3 effort
1 - USFD	13.00
2 - ANSYS	24.00
6 - UR1	2.00
7 - MDC	10.00
8 - PEN	29.00
9 - PHILIPS	11.00
12 - TU/e	18.00
Total	107.00

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D3.1	Software Components Specifications	8 - PEN	Report	Public	4
D3.2	Software Components Beta Release	8 - PEN	Other	Confidential, only for members of the consortium (including the Commission Services)	15
D3.3	ROM Tools Manual	2 - ANSYS	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.4	Software Components Candidate Release	8 - PEN	Other	Confidential, only for members of the consortium (including the Commission Services)	30

Description of deliverables

D3.1 Components specification
D3.2 Components beta release

D3.3 Reduced order modelling tools manual
D3.4 Components candidate release

D3.1 : Software Components Specifications [4]

Software Components Specifications

D3.2 : Software Components Beta Release [15]

Software Components Beta Release (Machine Learning Toolkit, Image Segmentation Toolkit, Systems Modelling Toolkit, Variation and Sensitivity Analysis Toolkit)

D3.3 : ROM Tools Manual [24]

Reduced Order Modelling Tools Operations Manual

D3.4 : Software Components Candidate Release [30]

Software Components Candidate Release

Schedule of relevant Milestones

Milestone number [18]	**Milestone title**	**Lead beneficiary**	**Due Date (in months)**	**Means of verification**
MS1	Specification phase complete	4 - CYFRONET	6	Specification phase complete
MS3	Assembly phase completed	9 - PHILIPS	15	Assembly Phase completed
MS4	Augmentation and Integration phase completed	5 - DHZB	28	Augmentation and Integration Phase completed
MS5	Candidate Release phase completed	11 - THERENVA	30	Candidate Release Phase completed

Work package number [9]	WP4	Lead beneficiary [10]	5 - DHZB
Work package title	DP Definition, Data Collection		
Start month	1	End month	36

Objectives

This work package collects the data on which the project depends. These data include clinical information from each patient, and population and epidemiological data that are used both for data inference and for data and model interpretation. All data will be appropriately annotated, organised and represented using the infrastructure developed in WP2.1. The WP4 objectives are:
1. To define the data that are important to underpin the decision support process
2. To specify the inclusion criteria for the study
3. To identify and recruit the cohort of patients on whom the decision support system will be tested.
4. To collect the data and to annotated, organise and represent it using the infrastructure developed in WP2.1. Such clinically relevant data will include:
* Demographic, laboratory and clinical data from each patient's Electronic Health Record.
* Acquired imaging, clinical, laboratory and ECG data before and after intervention.
* Epidemiological data from the published literature.
* Environmental data from pervasive monitoring.

Description of work and role of partners

WP4 - DP Definition, Data Collection [Months: 1-36]
DHZB , USFD, CATH, UR1, MDC, PEN, PHILIPS, STH , UBRIS
Task 4.1 Digital Patient Definition
Activity Leader: DHZB. Contact person: Prof Titus Kuehne titus.kuehne@dhzb.de

EurValve will develop a comprehensive DSS, maximally incorporating patient-specific data to provide as tailored a recommendation as possible, and key to the DSS design is the initial definition of the matching comprehensive data set that will inform the modelling and decision engine. This dataset must allow for information from current patient pathways (including imaging by CT and Echo, laboratory testing, and other clinical data) and also from anticipated future pathways, in particular MR imaging which drives the EurValve haemodynamic modelling process and is expected to enter clinical guidelines in due course.
This task will therefore identify all data that might be important to support the decision process for patients presenting with aortic or mitral valve disease, and will define the operations on these data to underpin the decision support mechanism.

Task 4.2 Study Design and Specification of Inclusion Criteria
Activity Leader: DHZB. Contact person: Prof Titus Kuehne titus.kuehne@dhzb.de

In a prospective clinical study design that has already been outlined (shown in figure 1 in section 1.2) a total of 120 patients will be enrolled in two patient groups.
Group 1: patients with aortic valve disease (n=60; per clinical centre n=20)
Group 2: patient with aortic valve disease (n=60; per clinical centre n=20). According to current hospital controlling data we expect approximately 30% of the patient to have combined aortic-mitral valve disease.
The sample size has been selected according to our power calculation (paired two tailed t-test comparing means of two independent variables) of a power of 0.8=1-4*alpha (alpha=0.05). Assuming a standard deviation of 9 mmHg with a clinical relevant difference of 3.5 mmHg the effect size of 0.39 and a resulting number of cases of 54 patients. The study will have the following structure at all clinical centres:
Visit 1: All patients will be investigated before valve intervention by imaging, ECG, laboratory tests, anthropometrics (blood pressure, body weight, clinical status etc.). These data will be used for modelling.
Operation (valve replacement/repair). In EurValve all patients will be treated according to current clinical guidelines. In the Berlin centre an additional myocardial biopsy will be performed in patients undergoing surgery, with the biomaterial being used for proteomic analysis.
Visit 2: After treatment patients will be followed-up undergoing the study protocol again. This allows comparing the modelled (predicted) against measured outcome data. After this validation of the models, a randomised controlled

experiment will be designed as part of T 6.4 in order to assess the efficiency of a DSS. In this second step a comparison between virtual decision making using a DSS and current clinical decision making will be carried out.
Since a DSS will be of most value in combined and complex cases, as well as in borderline cases further sub-group definitions and stratifications will be of particular interest, and thus be part of this task.

Task 4.3 Literature Data
Activity Leader: PEN. Contact person: Dr Herman ter Horst (Philips); herman.ter.horst@philips.com

This task will identify the literature relevant to the population of data fields that are necessary for the execution of the model but not measured on the individual patient, and will identify the literature relevant to the interpretation of measured and computed data in the context of diagnosis, prognosis, and decision support. As an example, based on literature this task will collect the information on comorbidities that is relevant in decision support for heart valve patients. This task also includes formatting, organisation, and extraction of data from literature sources using the tools provided by WP2. The task interfaces with T4.1, where the application-specific patient avatar will be defined.

Task 4.4 Environmental Data
Activity Leader: University of Bristol Contact person: Prof Ian Craddock Ian.Craddock@bristol.ac.uk

There is widespread acceptance that the explosion of interest in wearable technology will transform healthcare, especially outside the clinical environment. The traditional model of an occasional high precision clinical measurement of a parameter will increasingly be replaced by continuous measurement of activity data in the subject's normal daily life. Such data can be an important factor in the DSS, in better understanding the cardiovascular risks patients are subjected to in their daily lives, as well as in understanding the effect of clinical management decisions in the context of a range of lifestyles.
Building upon the SPHERE project at the UBRIS, Task 4.4 will consider the determination of the patient's physiological envelope in terms of activity types and levels from a low-cost, wrist-worn research wearable device. Unlike what would be possible with a commercial wearable, the wearable device will be tuned in both hardware and software to the requirements of EurValve's clinicians.
The project will need to advance algorithms that derive meaning from the raw accelerometer data in terms of activity type and level, specifically tailored to the activities of interest to clinicians (these might include activities such as Walking, Jogging, Climbing stairs, Vacuuming, Brushing teeth, Sitting & relaxing, Watching TV, Bicycling, Sleeping). State-of-the-art approaches for activity recognition are based on machine learning algorithms, the performance of which is dependent on the quality of the feature representation of the raw data. The features used in this Task will be computed from the raw data using signal processing techniques, and will include elementary time domain features including the mean and standard deviation, elementary frequency domain features including the entropy and spectral energy, as well as features manually designed by exploiting expert knowledge, and features discovered automatically from unsupervised data using state-of-the-art 'deep learning'129 strategies.
The approach for quantifying activity level will generally depend on the activity type. E.g. it may involve the stride, pace, and total number of steps when walking, as well as derived activity level aggregates (e.g. number of calories burned) over a day or peak activity levels within a day.
Thus the Task consists of the following subtasks:
• Subtask 4.4.1 Identification of target activities.
• Subtask 4.4.2 Physical Activity Sensing hardware design for energy constraint pervasive monitoring, and feature development.
• Subtask 4.4.3 Development of machine learning algorithms for activity type recognition and activity level quantification.
• Subtask 4.4.4 Initial testing, making use of the massively-instrumented SPHERE house in central Bristol to gather ground truth.
• Subtask 4.4.5 Two week sensor deployments in EurValve trial centres.

Task 4.5 Identification, Recruitment and Data Assembly for Clinical Cohort
Activity Leader: DHZB. Contact person: Prof Titus Kuehne titus.kuehne@dhzb.de

Description of process of recruitment, milestones. Transmission of data to warehouse designed and implemented in T2.1. This includes working with an image acquisition protocol (echo, MRI) that is feasible to perform to ensure continuous data quality throughout the whole project. This data from the hospital PACS will be made available in a pseudo- anonymised way. Furthermore other clinically relevant data points will be included in an eCRF. Imaging data will be pre-processed (4d flow reconstruction, volumetric measures) before being fed into the infra-structure.
Biomaterial will be acquired during heart surgery (an ethical approval to acquire and store such biomaterial has already been given from the ethical committee in Berlin). The material will be supplied to the project partner MDC where a proteomic analysis will be performed.

Partner Roles:
DHZB will lead the work package, identify (with the support of USFD), the data that will define the digital patient for this application, and co-ordinate the design of the study.
The Clinical Centres (DHZB, STHFT, Catharina) will recruit the patients and enter the data into the warehouse.
UBRISTOL will collect the environmental data to demonstrate the potential for inclusion of pervasive monitoring data in a personalised decision support environment.

Participation per Partner

Partner number and short name	WP4 effort
1 - USFD	2.00
3 - CATH	10.00
5 - DHZB	19.00
6 - UR1	2.00
7 - MDC	6.00
8 - PEN	7.00
9 - PHILIPS	3.00
10 - STH	10.00
13 - UBRIS	30.00
Total	89.00

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D4.1	Digital Patient Definition	5 - DHZB	Report	Public	3
D4.2	Clinical Cohort Specification	5 - DHZB	Report	Public	4
D4.3	Data Status Report	5 - DHZB	Report	Public	15
D4.4	Literature and Guidelines Report	8 - PEN	Report	Public	15
D4.5	Activity Monitoring Report	13 - UBRIS	Report	Confidential, only for members of the consortium (including the Commission Services)	15
D4.6	Activity Monitoring Data Analysis	13 - UBRIS	Report	Confidential, only for members of the consortium (including the Commission Services)	28

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D4.7	Data Summary and Review	5 - DHZB	Report	Public	30

Description of deliverables

D4.1 Digital Patient definition
D4.2 Cohort specification
D4.3 Data availability status report
D4.4 Literature and Guidelines analysis
D4.5 Activity Monitoring report
D4.6 Activity Monitoring analysis
D4.7 Data review

D4.1 : Digital Patient Definition [3]

Context-Specific Digital Patient Definition (Valve Assessment and Intervention)

D4.2 : Clinical Cohort Specification [4]

Clinical Cohort and Inclusion Criteria Specification

D4.3 : Data Status Report [15]

Data availability status report

D4.4 : Literature and Guidelines Report [15]

Literature and Guidelines Analysis and Recommendations Report

D4.5 : Activity Monitoring Report [15]

Activity Monitoring Hardware Deployment and Testing Report

D4.6 : Activity Monitoring Data Analysis [28]

Activity Monitoring Data Analysis

D4.7 : Data Summary and Review [30]

Comprehensive data summary and review

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS1	Specification phase complete	4 - CYFRONET	6	Specification phase complete
MS2	Data population commenced	5 - DHZB	9	Data warehouse population commenced at clinical centres
MS6	Final evaluation commenced	11 - THERENVA	33	Final Evaluation commenced

Work package number [9]	WP5	Lead beneficiary [10]	11 - THERENVA
Work package title	Decision Support System		
Start month	1	End month	36

Objectives

This work package develops the primary output of the project, the Decision Support System. Objectives:
1. To specify the requirements for, and technical content of, the DSS
2. To design an integrated system capable of co-operating with the computational infrastructure
3. To include a clinically-favoured Case-Based Reasoning system, in which the extensive historical data on previous patients is used to provide insights into possible current treatment alternatives
4. To build and deploy a comprehensive beta-release DS system
5. To respond to user experience, incorporating improvements in a final DSS release

Description of work and role of partners

WP5 - Decision Support System [Months: 1-36]
THERENVA, USFD, CATH, CYFRONET, DHZB , UR1, PEN, PHILIPS, STH , TU/e
Task 5.1 Decision Support System Specification
Activity Leader: Therenva. Contact person: Cemil Göksu cemil.goksu@therenva.com

This task will generate the formal description of the requirements to which the DSS should operate.
The DSS will be implemented as a plug-in within the framework of the EndoSize software, a commercially available CE-marked and FDA-approved modular platform developed by Therenva addressing the specific planning needs of endovascular and endovalvular procedures.
Built on the existing decision support tool, the DSS will operate on a stand-alone workstation and will be integrated to the already available planning workflow which includes currently a geometrical data extraction process, a standardised keypoints-based measurement process, and a procedure strategy process based on warnings relating to the indications for use of implant devices.
Interview meetings with the participating clinicians will be conducted in order to specify the features and interfaces the clinical DSS should present to be adopted and used efficiently in clinical routine.

Task 5.2 Integration of DSS with computational infrastructure
Activity Leader: CYFRONET (with STHFT) Contact person: Piotr Nowakowski ymnowako@cyf-kr.edu.pl

CYFRONET and STHFT will lead the integration of DSS with the computational infrastructure developed in WP2, using the application model selected for the DSS.
The goal of this task is to provision and maintain the necessary computational resources which will be required for the operation of DSS software. This task will first perform an analysis of the available computational infrastructures, including resources contributed by Project partners as well as bought-in resources (e.g. computational cloud hardware), then decide upon an optimal deployment strategy taking into account the quantitative resource requirements imposed by the Valve DSS.
Once a deployment plan is prepared this task will supervise its implementation. The DSS software will be deployed in three separate environments (testing, staging and production), enabling developers to carry out incremental upgrades without affecting the operation of the system. This task will also monitor resource usage, handle billing and produce periodic reports for the Consortium. Where required, the task will interface directly with developers of DSS software, advise on optimal deployment strategies and take part in joint implementation of services in a manner which best suits the chosen hardware platforms.

Task 5.3 Case Based Reasoning
Activity Leader: UR1-LTSI. Contact person: Pascal Haigron Pascal.Haigron@univ-rennes1.fr

The DSS will include the facility to provide Case Based Reasoning against the de-identified data held in the project data repositories. The CBR solving cycle is generally based on the following steps: retrieving, reusing, revising and retaining. In this project, the objective is to provide the practitioner with an easy interpretable selection of the most relevant cases according to the current candidate patient. The work will mainly deal with case retrieving. UR1-LTSI will focus on case similarity. Therenva will integrate the CBR facilities into the DSS.
A case is a contextualised piece of experience which can be represented in various forms to integrate the problem (situation) and the solution (action). The problem incorporates specific information which characterises the case

(e.g. patient age, ejection fraction, aortic annulus diameter, valve calcifications …) whereas the solution incorporates information for solving any particular problem (measures to consider, clinician decision process, outcome of the treatment). The significance and the type of input features will be also dependent on the available data (resulting or not from processing), modelling and statistical analysis for feature selection. Case definition, representation and similarity will be studied jointly with clinical experts by analysing targeted and relevant decision process with respect to available information. Different types of unstructured or structured memories for case representation can be considered (feature vectors, networks, decision trees, ...). In order to be scalable and compatible with the generic data repository infrastructure, indexed memories will provide the way to encapsulate the cases and make the link to the available data. In a context of heterogeneous and missing data, a large part of the work will be devoted to the study of similarity metrics which play an important role in case retrieval. In order to show how this type of system can be helpful for clinician, a first solution based on distance between feature vectors (e.g. a combination of global and local weighted distances between attribute-value pairs) will be developed. It will also be used for designing the user interface in order to easily interact with the system and to visualise in an interpretable way the summarised data derived from the retrieved cases. In addition, a more challenging solution will be studied. It will concern the proposition of new similarity metrics to overcome the problem of missing, uncertain or imprecise data (e.g. fuzzy measures) and to overcome the fact that the most important features to consider for the retrieval process is often context (e.g. patient) dependent. It will also concern the proposition of similarity metrics adapted to more structured memories (e.g. graph similarity measures).

Task 5.4 Decision Support System Beta version
Activity Leader: Therenva. Contact person: Cemil Göksu cemil.goksu@therenva.com

A preliminary version of the DSS will focus on operating rules on limited data - patient history data and follow-up data, as well as on specific morphological information extracted from imaging exams. This information (diameters, lengths, angulations, shape, etc.) will be provided by measurement and segmentation processes. The user interface will present comprehensive recommendations based on the set of rules. The beta version will be made available at PM24.

Task 5.5 Decision Support System final version
Activity Leader: Therenva. Contact person: Cemil Göksu cemil.goksu@therenva.com

The final version of the DSS will provide an extended set of patient data on which additional rules will operate, especially physiological data extracted from built-in patient-specific 3D CFD simulation capabilities.
It will also integrate the CBR capabilities and will get access to the remote de-identified cases to be presented to the clinicians as a result of the CBR retrieving process. Visualisation of the cases will be resulting from the specifications stage and may eventually include a summary of the patient data and follow-up, as well as key images. The final release will take place at PM36.

Partner Roles:
THERENVA will lead the workpackage and drive the specification and DSS construction activities.
UR1-LTSI will support the DSS with the case-based reasoning feature
PHILIPS will provide the machine-learning rules sets
CYFRONET and STHFT will provide support in the integration of the computational infrastructure, including access to the data warehouse, into the DSS.
USFD will provide support in the integration and operation of the systems physiology model.
TUE will provide support in the integration and operation of the systems physiology model.

Participation per Partner

Partner number and short name	WP5 effort
1 - USFD	6.00
3 - CATH	6.00
4 - CYFRONET	6.00
5 - DHZB	6.00
6 - UR1	21.00
8 - PEN	6.00
9 - PHILIPS	3.00

Partner number and short name	WP5 effort
10 - STH	6.00
11 - THERENVA	30.00
12 - TU/e	6.00
Total	96.00

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D5.1	Decision Support System Specification	11 - THERENVA	Report	Public	6
D5.2	Decision Support System Beta Release	11 - THERENVA	Other	Confidential, only for members of the consortium (including the Commission Services)	21
D5.3	Case-Based Reasoning Module	6 - UR1	Other	Confidential, only for members of the consortium (including the Commission Services)	21
D5.4	Decision Support System Candidate Release	11 - THERENVA	Other	Confidential, only for members of the consortium (including the Commission Services)	32

Description of deliverables

D5.1 DSS specification
D5.2 DSS beta release
D5.3 Case-based reasoning module
D5.4 DSS candidate release

D5.1 : Decision Support System Specification [6]

Decision Support System Specification

D5.2 : Decision Support System Beta Release [21]

Decision Support System Beta Release

D5.3 : Case-Based Reasoning Module [21]

Case-Based Reasoning Module

D5.4 : Decision Support System Candidate Release [32]

Decision Support System Candidate Release

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS1	Specification phase complete	4 - CYFRONET	6	Specification phase complete
MS3	Assembly phase completed	9 - PHILIPS	15	Assembly Phase completed
MS5	Candidate Release phase completed	11 - THERENVA	30	Candidate Release Phase completed
MS6	Final evaluation commenced	11 - THERENVA	33	Final Evaluation commenced

Work package number [9]	WP6	Lead beneficiary [10]	5 - DHZB
Work package title	DSS Operation		
Start month	1	End month	36

Objectives

WP6 will apply the DSS to the identified cohort of clinical cases. Key objectives are:
1. To operate the software components on the study cohort.
2. To add to the data warehouse the parameters derived from the computational operations.
3. To use the project's own database to infer parameters and rule sets.
4. To evaluate the operation of the DSS on the patient cohort
5. To evaluate the performance of the combined DSS and infrastructure system

Description of work and role of partners

WP6 - DSS Operation [Months: 1-36]
DHZB , USFD, ANSYS, CATH, CYFRONET, UR1, MDC, PEN, PHILIPS, STH , TU/e
Task 6.1 : Operation on Study Cohort
Activity Leader: USFD. Contact person: Prof Rod Hose (USFD); d.r.hose@sheffield.ac.uk

USFD will co-ordinate the application of the DSS to the study cohort, across the clinical centres. The operation of the DSS will include computation of derived data, such as morphology and haemodynamic characteristics, that will be entered into the data warehouse to complement the raw data entered directly by the clinical centres in task 4.3.

Task 6.2 : Rule Set Derivation, Study Cohort
Activity Leader: PEN. Contact person: Dr Herman ter Horst; herman.ter.horst@philips.com

The purpose of this task is to operate on the enhanced data provided by the study cohort to develop new knowledge for integration into the DSS work flow. This task will provide information that is relevant to clinicians and in the DSS in the management of heart valve patients, based on learning from data and on literature. The term rule set is broadly interpreted: for example, in addition to IF THEN rules based on literature also statements or assessments could be provided for use in the DSS, for example a statement derived by a learning program based on data to the effect that a patient is deteriorating.
This task interfaces with T3.1 where machine learning tools are developed, with T4.1, where the application-specific patient avatar will be defined, and with T4.3 where relevant literature is identified.

Task 6.3 : Evaluation of DSS applied to Study Cohort
Activity Leader: DHZB. Contact person: Prof Titus Kuehne titus.kuehne@dhzb.de

The individual clinical centres will report the results of the operation of the DSS on the study cohort, emphasising the ease-of-use, the effectiveness, and the potential clinical utility. DHZB will assemble these reports and produce a summary report.

Task 6.4: Evaluation of the Effectiveness of Modelling
Activity Leader: DHZB. Contact person: Prof Titus Kuehne titus.kuehne@dhzb.de

DHZB will design a randomised controlled experiment that assesses the effectiveness of supported decision making. It is based on the modelling and DSS data provided. Once the simulated models (based on known interactions and newly acquired from machine learning tools) have been validated against the actual patient specific outcome they will provide the opportunity to simulate several (virtual) options of post-interventional outcome. Within this experiment there will be a comparison of virtual decision making using a DSS against current clinical decision making based on clinical outcome data.

Task 6.5 Evaluation of combined infrastructure and DSS software platform
Activity Leader: CYFRONET. Contact person: Marek Kasztelnik, m.kasztelnik@cyfronet.pl

CYFRONET will lead the testing and evaluation procedure of infrastructure and software developed for DSS. This will include integration tests, acceptance testing and performance evaluation
In the scope of this task we will be constantly evaluating the work done by work packages 2 and 5 in order to guarantee that it is on track with the end user requirements. We will prepare methodologies and guidelines how DSS platform should be developed and deployed using continuous delivery methodology. We will set up environment which will

automatically test new version of the system and when defined metrics will be fulfilled by new software version (e.g. all unit, smoke and integration tests passed, response time for critical services is below defined threshold, code quality metrics are met), it will be automatically released and deployed into production environment without interrupting normal system usage.
Work done in the scope of this task will be organised as follows: at the beginning we will evaluate state of the art of the continuous delivery methodology and examine existing technologies created for this purpose (such as Github1 connected with Travis2 continuous integration and Codeship3). Next, we will extract most important best practices and prepare guidelines for other packages which will be responsible for developing new software. Basing on the guideline, the testing, staging and production environments with accompanying tools will be set up and shared with other work packages. These environments will be used for continuous delivery of created DSSs. The final step will be to prepare set of smoke tests4 and integration tests which will be constantly executed on staging and production environment and notifying developers about any issue or violations (e.g. response time to high) occurred.
1 https://github.com; 2 https://travis-ci.org; 3 https://codeship.com; 4 http://en.wikipedia.org/wiki/Smoke_testing_(software)

Partner Roles:
DHZB will lead the workpackage, directing the application of the DSS to clinical data.
USFD will organise the process
PEN will construct the relevant rule set
CYFRONET will coordinate the assessment of the completed DSS/platform system

Participation per Partner

Partner number and short name	WP6 effort
1 - USFD	9.00
2 - ANSYS	6.00
3 - CATH	8.00
4 - CYFRONET	3.00
5 - DHZB	12.00
6 - UR1	2.00
7 - MDC	8.00
8 - PEN	15.00
9 - PHILIPS	7.00
10 - STH	8.00
12 - TU/e	6.00
Total	84.00

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D6.1	Model-based Data Augmentation Report	1 - USFD	Report	Public	28
D6.2	Model-based Learning Report	8 - PEN	Report	Public	28

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D6.3	Final DSS Evaluation Report	5 - DHZB	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D6.4	Platform Evaluation Report	4 - CYFRONET	Report	Confidential, only for members of the consortium (including the Commission Services)	36

Description of deliverables

D6.1 Model-based data augmentation report
D6.2 Model-based learning report
D6.3 Final DSS evaluation report
D6.4 Platform evaluation report

D6.1 : Model-based Data Augmentation Report [28]

Model-based Data Augmentation Report

D6.2 : Model-based Learning Report [28]

Model-based Learning Report

D6.3 : Final DSS Evaluation Report [36]

Final DSS Evaluation Report

D6.4 : Platform Evaluation Report [36]

Platform Evaluation Report

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS4	Augmentation and Integration phase completed	5 - DHZB	28	Augmentation and Integration Phase completed
MS6	Final evaluation commenced	11 - THERENVA	33	Final Evaluation commenced

Work package number [9]	WP7	Lead beneficiary [10]	11 - THERENVA
Work package title	Exploitation		
Start month	1	End month	36

Objectives

WP7 is responsible for all aspects of the exploitation of the software system. This has two essential components:
1. Market: Health economics assessment and market evaluation
2. Regulation: Assessment, strategy and planning for all aspects of regulatory approval

Description of work and role of partners

WP7 - Exploitation [Months: 1-36]
THERENVA, USFD, ANSYS, PEN, PHILIPS, UBRIS
Task 7.1 Market Assessment and Evaluation
Activity Leader: THERENVA. Contact person: Cemil Göksu cemil.goksu@therenva.com
The task will be structured around subtasks, as follows:
Subtask 7.1.1. Evaluation and Exploitation planning (PM13 - PM36]
Exploitation activities are discussed in detail in section 2.2.2. Topic summary:
* Alpha Solution
* Remote availability
* Beta Solution
* Go-to-market strategy

Subtask 7.1.2. General Dissemination (PM01 – PM36)
In this subtask we will implement the Dissemination strategy described earlier, disseminating the outcome of the project to the different stakeholders. Methodologies are listed below:
* Web systems
* Slide Deck
* Conferences & Events
* Scientific Articles
* Communications
* Press Releases
* White Papers
* Video
* Social Media
* Collaterals
* Workshop
We will record, quantify and further evaluate the impact of these activities.

Subtask 7.1.3: Development of an exploitation strategy (month 1 - month 36; all partners)
Commercial partners will work with project technology partners to develop an plan for the onward exploitation of the principal and component elements of the project.

Task 7.2 Regulatory Environment
Activity Leader: USFD. Contact person: Prof P.V.Lawford@sheffield.ac.uk
USFD, working closely with THERENVA, will review the regulatory framework for such software products, ensuring compliance with appropriate requirements and establishing where additional standards will be required in due course.

Partner Roles:
THERENVA will lead the work package and perform market analysis and dissemination
ANSYS will provide market analysis and dissemination
PHILIPS will provide market analysis and dissemination
PEN will provide market analysis and dissemination
USFD will provide regulatory detail

Participation per Partner

Partner number and short name	WP7 effort
1 - USFD	9.00
2 - ANSYS	5.00
8 - PEN	1.00
9 - PHILIPS	1.00
11 - THERENVA	16.00
13 - UBRIS	6.00
Total	38.00

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D7.1	Exploitation Initial Report	11 - THERENVA	Report	Confidential, only for members of the consortium (including the Commission Services)	12
D7.2	Exploitation Interim Report	11 - THERENVA	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D7.3	Exploitation Final Report	11 - THERENVA	Report	Confidential, only for members of the consortium (including the Commission Services)	36

Description of deliverables

D7.1 Initial report on dissemination and regulatory processes
D7.2 Interim report on dissemination and regulatory processes
D7.3 Final report on dissemination and regulatory processes

D7.1 : Exploitation Initial Report [12]

Initial report on dissemination exploitation & regulation

D7.2 : Exploitation Interim Report [24]

Interim report on dissemination exploitation & regulation

D7.3 : Exploitation Final Report [36]

Final report on dissemination exploitation & regulation

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS6	Final evaluation commenced	11 - THERENVA	33	Final Evaluation commenced

1.3.4. WT4 List of milestones

Milestone number [18]	Milestone title	WP number [9]	Lead beneficiary	Due Date (in months) [17]	Means of verification
MS1	Specification phase complete	WP2, WP3, WP4, WP5	4 - CYFRONET	6	Specification phase complete
MS2	Data population commenced	WP2, WP4	5 - DHZB	9	Data warehouse population commenced at clinical centres
MS3	Assembly phase completed	WP3, WP5	9 - PHILIPS	15	Assembly Phase completed
MS4	Augmentation and Integration phase completed	WP3, WP6	5 - DHZB	28	Augmentation and Integration Phase completed
MS5	Candidate Release phase completed	WP2, WP3, WP5	11 - THERENVA	30	Candidate Release Phase completed
MS6	Final evaluation commenced	WP2, WP4, WP5, WP6, WP7	11 - THERENVA	33	Final Evaluation commenced

1.3.5. WT5 Critical Implementation risks and mitigation actions

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
R1	Fragmentation of tasks into a series of separated activities within each WP	WP1	The project's workplan has been divided into cross-cutting workpackages. The EurValve infrastructure acts as an integrator - rather than developing a number of workflows or applications, the project is dedicated to implementing and deploying a coherent system serving a specific purpose.
R2	Decisions of the Project Board remote from developers, delayed implementation	WP1	The project has instituted an 'Implementation Group whose responsibility is to ensure that decisions are translated into actions.
R3	EurValve infrastructure does not meet requirements	WP2	Define test scenarios early and foster tight collaboration between the developers and users.
R4	EurValve security mechanisms do not meet expectations	WP2	Security technology is well-proven in similar environments to those featuring in the project
R5	Requirements in specification do not reflect true need	WP3	Workflow descriptions delivered early to detect problems quickly and demand more complex scenarios from the workflow co-ordinators
R6	Adoption of incompatible development platforms	WP3	To avoid incompatibility, a set of allowed (and interoperable) development technologies will be defined
R7	Technological solutions too difficult to deploy or to use	WP3	The project will demand a minimum level of documentation associated with all software releases.
R8	Failure to deliver any particular facility	WP3	The general principle is to deliver a series of services that support the DSS process. A degree of redundancy and interoperability is a fundamental property of the services that we will build. Should any critical component not

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
			be delivered the PB will identify alternative solutions and redeploy resources accordingly.
R9	Datasets do not become available to the project at the expected time or in the expected quantity.	WP4	The first data will come from existing data sets. If any project partners fail to deliver to data provision commitments in the DoW resources will be diverted to assist
R10	Environment data proves difficult to use effectively	WP4	Integration of such data is familiar to the partners concerned; flexible engineering of this data interface will be included from the outset
R11	Delay in the implementation or deployment of the necessary technologies emerging from the different technological activities	WP5	This is a standard management risk. The mitigation plan will be to prioritise those components with higher impact in order to service the cDSS. Components already available from other projects can be made available as services without excessive effort.
R12	Problems with stability and reliability of software technologies used for development of executable system	WP5	A thorough analysis of state-of-the art technologies together with performance and stability testing from the early stage of the development, coupled with software engineering procedures in Tasks 3.x to ensure quality of the product.
R13	Technical solutions produced by different technical activities do not integrate; the system does not operate effectively as a whole	WP5	A specific Implementation group is set up within the management structure, to include the technical leads for each of the core components. This group will meet regularly to discuss the very detailed technical implementation plans for all components before development work begins so each software provider has a chance to understand and review all technologies. This will

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
			avoid the most common problem in large ICT projects: poor integration due to lack of detailed specification where standards do not exist
R14	Difficulties in handling and integrating technologies required by models into a coherent environment.	WP5	Use of container and virtualisation technologies together with service oriented architecture model to ensure proper isolation between components and to provide a common abstraction layer over heterogeneous technologies, relying on the expertise of CYFRONET team.
R15	Low transfer rates of data being visualised resulting in playback with lags	WP5	Constant acceptance tests for final user experience will be a part of the visualisation development process with reasonable thresholds established for the pilot use cases.
R16	Failure to combine different multiscale models in a coherent visual form	WP5	A fall-back to showing different scales separately with a synchronised timeline will be also part of the visualisation development process.
R17	Quality of developed software is inadequate	WP6	Project partners have strong software engineering background and are already proven to deliver high quality software. Project will employ tools rejecting software when defined conditions are not met (e.g. software performance is below defined threshold, accepted code style is violated).
R18	Unit, smoke, integration and regression tests inadequate	WP6	The project will provide in the early stage a set of guidelines showing how software should be tested, including examples how it will improve software development process. Project will deliver integrated environment responsible for automatic software testing and

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
			rejecting new version when code quality is not good enough.
R19	Partners fail to cooperate on the evaluation tasks	WP6	Project coordinator has set aside particular efforts for each work package to contribute to the project evaluation and participate in formulating the exploitation strategies.
R20	Failure to achieve market interest in the system	WP7	The project has allocated a budget to exploitation, to encourage pilot users to begin to engage with the infostructure. As the functional utility of the developed services increases, and as virtual collaborations form, it is anticipated that this particular risk will reduce over time.
R21	Regulatory conflict identified	WP7	Partners are extremely familiar with the regulatory landscape. Any incompatibility is likely to be minor and quickly resolved. To minimise the risk, engagement will take place at an early stage of the project

1.3.6. WT6 Summary of project effort in person-months

	WP1	WP2	WP3	WP4	WP5	WP6	WP7	Total Person/Months per Participant
1 - USFD	17	5	13	2	6	9	9	61
2 - ANSYS	1	0	24	0	0	6	5	36
3 - CATH	2	0	0	10	6	8	0	26
4 - CYFRONET	2	47	0	0	6	3	0	58
5 - DHZB	2	21	0	19	6	12	0	60
6 - UR1	2	1	2	2	21	2	0	30
7 - MDC	2	0	10	6	0	8	0	26
8 - PEN	2	0	29	7	6	15	1	60
9 - PHILIPS	2	0	11	3	3	7	1	27
10 - STH	2	24	0	10	6	8	0	50
11 - THERENVA	2	0	0	0	30	0	16	48
12 - TU/e	2	0	18	0	6	6	0	32
13 - UBRIS	2	0	0	30	0	0	6	38
Total Person/Months	40	98	107	89	96	84	38	552

1.3.7. WT7 Tentative schedule of project reviews

Review number [19]	Tentative timing	Planned venue of review	Comments, if any
RV1	18	Brussels	
RV2	36	Brussels	

1.4. Ethics Requirements

Ethics Issue Category	Ethics Requirement Description
HUMANS	- The applicant must provide more details on the incidental finding policy (see section 5 which states that the informed consent form will provide details on the procedures on incidental findings management, but no such evidence is given in the proposal).
HUMANS	- The applicant must specify if children are to be included in the research.
HUMANS	- The applicant must provide more details on the sex, age, and ethnicity of the participants recruited in the research.
PROTECTION OF PERSONAL DATA	- A specific description of data management, identity protection and data destruction must be given by the applicant. The proposal only describes the general principles regarding data protection management, but no details on the real procedures that will be adopted is given.
HUMAN CELLS / TISSUES	- The applicant must provide copies of ethics approvals to collect tissue samples as soon as they are available. The applicant declared that an ethical approval to collect tissue samples was already given by an ethical committee in Berlin, but no evidence of this is given. In other cases (section 5), the applicant declared that ethical approval requests will be submitted to relevant local authorities.
HUMANS	- If children are to be included in the research, the applicant must clarify how consent/assent will be ensured.

1. Project number

The project number has been assigned by the Commission as the unique identifier for your project. It cannot be changed. The project number **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

2. Project acronym

Use the project acronym as given in the submitted proposal. It can generally not be changed. The same acronym **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

3. Project title

Use the title (preferably no longer than 200 characters) as indicated in the submitted proposal. Minor corrections are possible if agreed during the preparation of the grant agreement.

4. Starting date

Unless a specific (fixed) starting date is duly justified and agreed upon during the preparation of the Grant Agreement, the project will start on the first day of the month following the entry into force of the Grant Agreement (NB : entry into force = signature by the Commission). Please note that if a fixed starting date is used, you will be required to provide a written justification.

5. Duration

Insert the duration of the project in full months.

6. Call (part) identifier

The Call (part) identifier is the reference number given in the call or part of the call you were addressing, as indicated in the publication of the call in the Official Journal of the European Union. You have to use the identifier given by the Commission in the letter inviting to prepare the grant agreement.

7. Abstract

8. Project Entry Month

The month at which the participant joined the consortium, month 1 marking the start date of the project, and all other start dates being relative to this start date.

9. Work Package number

Work package number: WP1, WP2, WP3, ..., WPn

10. Lead beneficiary

This must be one of the beneficiaries in the grant (not a third party) - Number of the beneficiary leading the work in this work package

11. Person-months per work package

The total number of person-months allocated to each work package.

12. Start month

Relative start date for the work in the specific work packages, month 1 marking the start date of the project, and all other start dates being relative to this start date.

13. End month

Relative end date, month 1 marking the start date of the project, and all end dates being relative to this start date.

14. Deliverable number

Deliverable numbers: D1 - Dn

15. Type

Please indicate the type of the deliverable using one of the following codes:

R	Document, report
DEM	Demonstrator, pilot, prototype
DEC	Websites, patent fillings, videos, etc.
OTHER	

16. Dissemination level

Please indicate the dissemination level using one of the following codes:

PU	Public

CO	Confidential, only for members of the consortium (including the Commission Services)
EU-RES	Classified Information: RESTREINT UE (Commission Decision 2005/444/EC)
EU-CON	Classified Information: CONFIDENTIEL UE (Commission Decision 2005/444/EC)
EU-SEC	Classified Information: SECRET UE (Commission Decision 2005/444/EC)

17. Delivery date for Deliverable

Month in which the deliverables will be available, month 1 marking the start date of the project, and all delivery dates being relative to this start date.

18. Milestone number

Milestone number:MS1, MS2, ..., MSn

19. Review number

Review number: RV1, RV2, ..., RVn

20. Installation Number

Number progressively the installations of a same infrastructure. An installation is a part of an infrastructure that could be used independently from the rest.

21. Installation country

Code of the country where the installation is located or IO if the access provider (the beneficiary or linked third party) is an international organization, an ERIC or a similar legal entity.

22. Type of access

VA	if virtual access,
TA-uc	if trans-national access with access costs declared on the basis of unit cost,
TA-ac	if trans-national access with access costs declared as actual costs, and
TA-cb	if trans-national access with access costs declared as a combination of actual costs and costs on the basis of unit cost.

23. Access costs

Cost of the access provided under the project. For virtual access fill only the second column. For trans-national access fill one of the two columns or both according to the way access costs are declared. Trans-national access costs on the basis of unit cost will result from the unit cost by the quantity of access to be provided.

EurValve

Title of Proposal

EurValve Personalised Decision Support for Heart Valve Disease

List of Changes

	Date	Pt	Section	Description	Differs from
1	10-Sep-15	A	Workpackage Effort	Effort allocations to PHILIPS and PEN corrected	Proposal
2	10-Sep-15	A	Workpackage Effort	Effort/WP distribution to UR1 corrected	Proposal
3	10-Sep-15	A	WP3 & 4	Activity allocation between PHILIPS and PEN corrected	Proposal
4	10-Sep-15	A	Indirect costs	All partners' indirect costs adjusted slightly; net result MDC +€14k	Proposal
5	10-Sep-15	B	Tables 3.1a/b/c	Tables removed	Proposal
6	10-Sep-15	B	Tables 3.2a/b	Tables removed	Proposal
7	10-Sep-15	B	Table 3.4a	Table removed (Note that the original table contained errors)	Proposal
8	17-Sep-15	B	Section 3.4	Total effort corrected	Part B 1v0
9	17-Sep-15	B	Section 4.3	Section added	Part B 1v0
10	17-Sep-15	B	(Multiple)	Beneficiary naming made consistent	Part B 1v0
11	05-Oct-15	B	Section 5.1	Ethics responses added to main text	Part B 1v0
12	09-Oct-15	B	Section 3.4.2	Cost ratio explanation added for beneficiary #4, updated for #7	Part B 1v1

Table of Contents

1. Excellence

EurValve will develop and deploy a clinically-compliant Decision Support System for the management of Valvular Heart Disease.

Valvular Heart Disease (VHD) currently affects 2.5% of the population, but is overwhelmingly a disease of the elderly and consequently on the rise. The prevalence is up to 13% in those over the age of 75, and the population beyond the age of 85 is set to nearly double in 2028[1]. It is dominated by two conditions, Aortic Stenosis and Mitral Regurgitation - both associated with significant morbidity and mortality, yet which pose a truly demanding challenge for treatment optimisation. By combining multiple complex modelling components developed in recent EC-funded research projects, a comprehensive, clinically-compliant decision-support system will be developed to meet this challenge, by quantifying individualised disease severity and patient impairment, predicting disease progression, ranking the effectiveness of alternative candidate procedures, and optimising the patient-specific intervention plan. This algorithmically-driven process will dramatically improve outcomes and consistency across Europe in this fast-growing patient group, maximising individual, societal and economic outcomes.

1.1 Objectives

Clinical Motivation and the Information Challenge: The timing and nature of interventional treatment is crucial in valve disease, but it remains a major challenge in current clinical practice[2,3]. According to databases, in the EU more than 70.000 valves are replaced or repaired per year (www.EACTS.org). EurValve will implement, test and validate a modelling based decision support system (DSS) for aortic and mitral valve diseases that allows simulating, comparing and understanding the effects (outcomes) and risks of different treatment strategies. In addition the DSS will improve our knowledge of disease mechanisms by applying a holistic assessment of cardiovascular function that includes hemodynamic data at all cardiovascular compartments (ventricle, valve, vessels) and multiscale components that couple organ with cell function.

We believe that the DSS will have major impact on patients with:

- Borderline indications for treatment (valve replacement/repair)
- Complex hemodynamic conditions such as combined aortic-mitral valve disease
- Valve geometries that are subject to valve repair

Timing of valve intervention: Operating on patients too late carries the risk of development of irreversible heart failure. Operating too early exposes patients to unnecessary risks and adverse events, conceivably causing short (e.g. valve thrombosis) or long term sequelae (e.g. early valve degeneration). According to the current National and European guidelines, medical decision making is, however, limited to the assessment of clinical symptoms, blood pressures and diagnostic imaging of global pump function (ejection fraction and ventricular chamber size)[4,5]. In addition, the valve opening area is used in settings where the ventricle cannot build up pressures across the valve (e.g. by combined aortic stenos and mitral insufficiency or global LV dysfunction). The planned DSS shall go clearly beyond such gross parameters by looking at the cardiovascular system at a more holistic and multi-scale way. In addition, the DSS shall allow for better personalisation of treatment strategies.

Type of valve intervention: In valve disease, many variations of repair/replacement techniques have been used with varying success rates in terms of perioperative mortality, preservation of postoperative ventricular function or long-term morbidity[6]. More recently, percutaneous methods for replacement of the pulmonary[7] , aortic valve[8] or tricuspid valve[9] or clips of the mitral valve[10] have been successfully introduced. These catheter based techniques were also pioneered by our institutions. There is consensus, that different types of valve prosthesis (size, shape) or repair techniques will have different functional results[11,12]. The planned DSS will allow for *in-silico* simulation of different treatment options and thus allow comparing their immediate hemodynamic outcome.

[1] d'Arcy et al. 2011
[2] McMurray et al. 2012
[3] Achenbach et al. 2012
[4] Vahanian et al. 2012
[5] Baumgartner et al. 2010
[6] Lung et al. 2003
[7] Eicken et al. 2011
[8] Fauchère et al. 2014
[9] Roberts et al. 2011
[10] Gaemperli et al. 2012
[11] Carlsson et al.2012
[12] Mahedevia et al. 2014

Holistic haemodynamic assessment beyond pressure gradients and volume load: The reduction of pressure and/or volume overload is currently the main argument for valve replacement because a reduced workload of the heart is thought to be a precondition for reverse myocardial remodelling. However, changes in pressure and volume load can have many secondary effects on the cardiovascular system that are important to understand and predict in borderline and complex hemodynamic conditions. It is a well-known problem that in aortic stenosis combined with mitral valve insufficiency it is difficult to predict how the diseased ventricle is able to cope with the changes in ventricular load. In addition, different types of valve replacement (mechanical, biological stented or stentless) and/or repair may induce specific blood flow profiles in the ventricle and aorta (e.g. change of kinetic energy or the wall shear stress, swirl and turbulence level, respectively), which in turn result in different pump efficiency or trigger acute vascular adaption and vastly affect long term remodelling. This has direct impact, amongst others on wall compliance, vascular resistance and pressure fields in the aorta – all these factors determine the workload that is imposed to the heart. Thus for a DSS it is essential to have information systematically available that take into account the complex hemodynamic interplay at all cardio-vascular components (heart chambers, valve, aorta and arterial vessels).

Multiscale effects – coupling of organ and cell function: In addition to the above mentioned hemodynamic effects of valve intervention at all compartments (ventricle, valve, vessel), a DSS should also take into account interactions that take place at the different biological scales. To better "predict" the course of myocardial remodelling the planned DSS will integrate information that comes from the tissue and cell level. Modern imaging by Magnetic Resonance T1-mapping provides quantitative information about fibrous tissue content that can be used in the models of organ mechanics. In addition, tissue samples that are gained during surgery allow performing proteomics of the cardiomyocyte. Models that use such patient-specific proteomics as input parameters allow the simulation of myocyte contractility and elastance in the united cell structures of a given patient. This information can be integrated back to the models at an organ level. This is an important step to recognise the complex interplay of the medical, physiological and biological processes that determine the prognosis for each individual patient.

The primary objectives of the DSS developed in EurValve will be to address these challenges and to apply and test in clinical studies of patients with aortic and mitral valve disease modelling tools for:

- Virtual surgery: In-silico testing of valve replacement by different valve prosthesis (size, shape, mechanical, biological) or repair by different repair techniques (virtual surgery based on valve segmentation)
- Simulate for a given patient the acute hemodynamic effects that different valve replacement/repair techniques have in a given patient. Importantly, the hemodynamic models will include the entire cardiovascular systems (left heart chambers, valves, aorta and arterial vessels)
- In addition, the DSS will account for multi-scale effects of myocardial remodelling. Models of the cardiomyocytes that are based on proteomics will be applied and coupled to the whole organ hemodynamic models
- The parameters derived from the models will be validated against parameters measured by current gold standards. Once simulated models have been validated the comparative effectiveness of supported decision making versus current clinical guidelines will be assessed.

From a technical perspective the DSS will facilitate:

- Representation, annotation, integration and visualisation of heterogeneous data from multiple sources.
- Inference of missing data where measurements are unavailable for a specific patient, based on population data from the published literature and by machine learning.

Sub-objectives are:

- Adaptation and exploitation of an existing computational infrastructure to facilitate the integration of the data sources and the construction of a *digital patient* that contains, in numerical form, all of the data necessary for operation of the decision support system in the context of heart valve disease.
- Publication of anonymised and aggregated metadata that describes the data content to facilitate exploitation by the clinical research community.
- Formal evaluation of the sensitivity of the DSS output to the variation and uncertainty of the model inputs.

The **target user** of this Decision Support System is the **healthcare professional**, in this case the surgeon or cardiologist, who will make the decision on the nature and timing of the intervention.

The major advance of this system over current practice is that it **integrates and interprets all heterogeneous data available about the patient, integrates population data where needed, and provides a consistent, repeatable, quantitative and auditable record of the information that contributes to the decision process.**

Clinical Goals and Study Design

The management of heart valve patients within the EU is carried out with reference to the recommendations of the Guidelines on the Management of Valvular Heart disease, an output of a Joint Task Force from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). These clinical guidelines have also been formalised by the participation of the clinical EurValve consortium members (Dr. Falk, DHZB)[13] .

Current guidelines conclude that improved scoring systems for predicting risks and outcomes of valve surgery and catheter based procedures are highly desirable. At present they 'limit' medical decision to the assessment of clinical symptoms, arterial blood pressures and global pump function (ejection fraction and ventricular chamber size). By their nature, such gross parameters yield a large range of thresholds and are subject to high inter-individual variability; consequently they do not reflect the complete pathophysiological state in a given patient.

Study design: In the EurValve initiative we will implement and test a DSS for aortic and mitral valve replacement/repair. Testing will be done within a prospective clinical study, the study design is shown in figure 1. Details about the study design are provided in WP4. Not all of the assessments listed will be performed on every patient, but sufficient to support the analysis processes. In brief: A total of 120 patients shall be enrolled in two subgroups:

- Group 1: patients with aortic valve disease (N=60; per clinical centre N=20)
- Group 2: patients with mitral valve disease (N=60; per clinical centre N=20). According to current hospital controlling data we expect approximately 30% of the patient to have combined aortic-mitral valve disease.

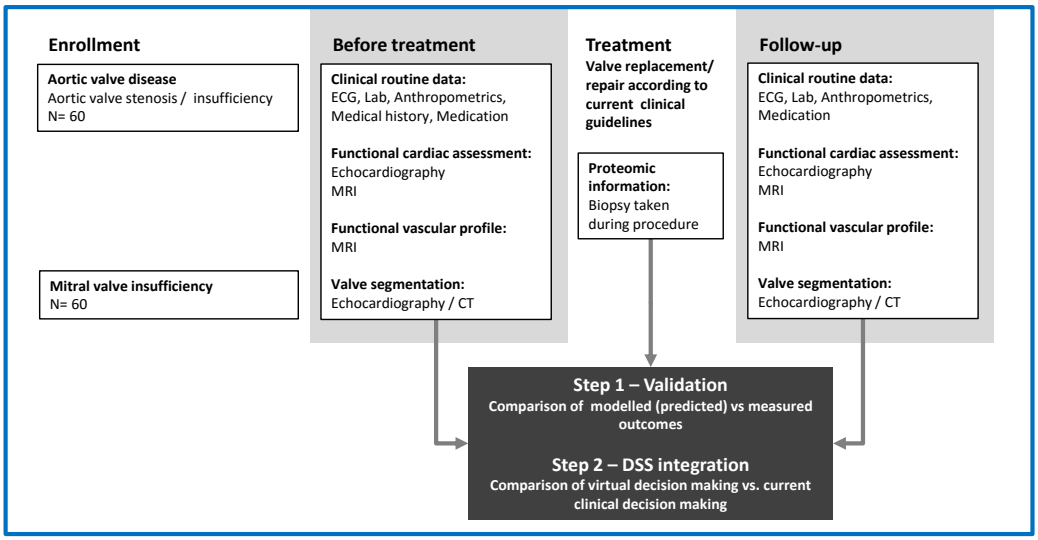

Figure 1 Prospective clinical study design

The study will have the following visits at all clinical centres:

- Visit 1: All patients will be investigated before valve intervention by imaging, ECG, laboratory tests, anthropometrics (blood pressure, body weight, clinical status etc.). These data will be used for modelling.
- Operation (valve replacement/repair). In EurValve all patients will be treated according to current clinical guidelines. In the Berlin centre an additional myocardial biopsy will be performed in patients undergoing surgery, with the biomaterial being used for proteomic analysis.
- Visit 2: After treatment patients will be followed-up undergoing the study protocol again. This allows comparing the modelled (predicted) against measured outcome data. After this validation of the models, a randomised controlled experiment will be designed as part of WP 6 in order to assess the efficiency of a DSS. In this second step a comparison between virtual decision making using a DSS and current clinical decision making will be carried out.

[13] Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC)1; European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451-96. doi: 10.1093/eurheartj/ehs109. Epub 2012 Aug 24.

1.1.1 Aortic Valve Disease

Aortic Stenosis (AS) is the most common valvular heart disease in both, the EU and the USA and it is predominantly a disease associated with calcification of the aortic valve in old age (estimated 2% - 7 % of the population over 65). For younger patients the most common underlying factor is congenital bicuspid valve disease.

Echocardiography is the primary tool to confirm the presence of AS and the degree of calcification, to assess LV function and wall thickness and to provide prognostic information. Doppler echocardiology provides information on severity. Valve area is theoretically the best measure of AS but may be operator dependent and thus should be considered in the light of other factors such as; degree of calcification, flow rate, pressure gradient, LV function, size and wall-thickness, blood pressure and functional status.

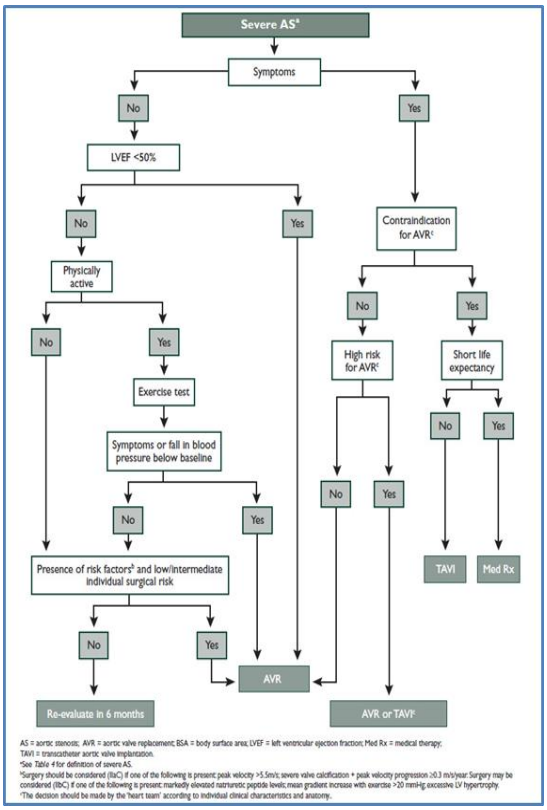

Figure 2: Example flow chart for management of Severe Aortic Stenosis[14]

Aortic valve replacement is the standard therapy for severe AS. Early replacement is recommended for all symptomatic patients with severe AS who are considered suitable for surgery as the disease is progressive and there is no medical therapy that is able to improve outcome. Operative mortalities range from ~1-8 % depending on age. Other factors, relevant to the timing of intervention, that increase risk include; increased age, functional class, emergency operation, LV dysfunction and pulmonary hypertension. Whilst surgery has been shown to prolong life and improve quality of life many patients are not offered it. Balloon valvuloplasty alone has a very limited role in treatment of adults with AS, as the risk of complications, and the reccurrence of disease is high. Transcatheter aortic valve implantation (TAVI) is usually beneficial for high risk patients but is not available at all centres and the long-term durability of TAVI valves has yet to be established. Management of asymptomatic patients with severe AS is controversial, and there is no data to support early replacement in asymptomatic patients with very severe AS.

Aortic regurgitation (AR) is the second most form of aortic valve disease. In many patients (e.g. with bicuspid aortic valves) AS is combined with AI Patients with AS. Chronic and severe volume overload due to AR and symptoms has, if left untreated, poor long-term prognosis.

Once symptoms become apparent, mortality in patients without surgical treatment may be as high as 10–20% per year. According to the ESC guidelines, in asymptomatic patients an LV end-systolic diameter (LVESD) of 50 mm is an indication for valve intervention. In patients with bicuspid aortic valve the size of the aorta is additional indication for operation (at the level of the ascending aorta).

[14] Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC)1; European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451-96. doi: 10.1093/eurheartj/ehs109. Epub 2012 Aug 24.

1.1.2 Mitral Valve Disease

Mitral regurgitation (MR) is the second most frequent valve disease in the EU. There are two types: primary which relates to pathology of the valve components, and secondary in which the valve is in a normal state but the supporting apparatus - the annulus or papillary muscles - are damaged by disease. A reduced incidence of rheumatic fever and an increased lifespan in European countries have also changed the major causes auf MR, and degenerative MR has now become *the most common.*

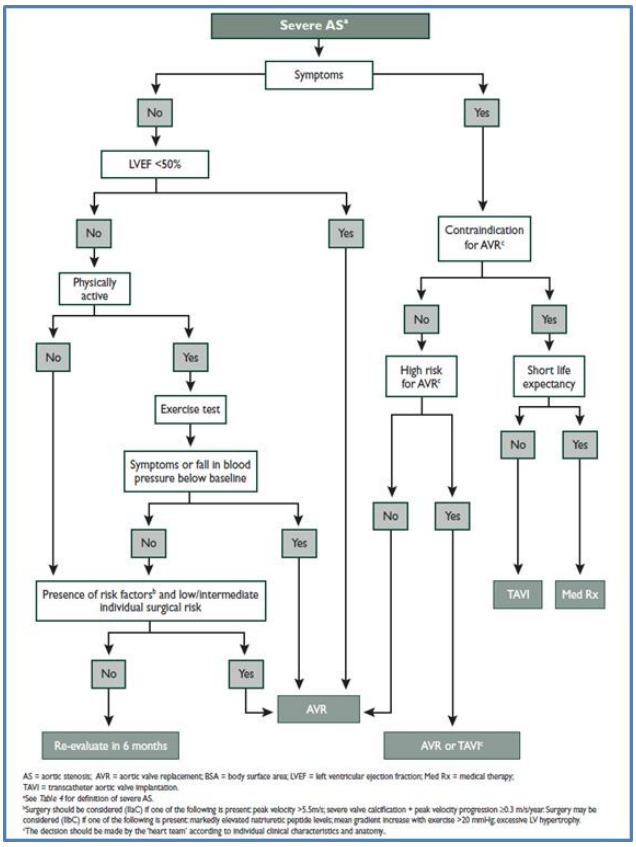

Figure 3: Example flow chart for management of severe chronic mitral regurgitation ([20])

For asymptomatic patients an estimated 5-year rate of death from any cause has been reported in 22% of cases.[15] There is a trend that valve repair is preferred over valve replacement in surgical therapies. In addition, transcatheter valve repair techniques are increasingly used that were also pioneered by our institutions. As stated, many variations of repair/replacement techniques have been used with varying success rates in terms of perioperative mortality, preservation of postoperative ventricular function or long-term morbidity[16]. More recently, percutaneous methods for replacement of the mitral valve[17] have been successfully introduced. There is consensus, that different types of valve prosthesis (size, shape) or repair techniques will have different functional results[18,19]. The planned DSS will allow for *in-silico* simulation of different treatment options and thus allow comparing their immediate hemodynamic outcome. In addition, the DSS is also expected to simulate the outcome in complex cases of mitral disease, e.g. in patients that have combined AS and MR. We expect that in our study population (see WP4) approximately 30% of the patients will have combined AS-MR.

1.2 Relation to the Work Programme

This proposal is targeted at PHC-30, *Personalising Health and Care: Digital representation of health data to improve disease diagnosis and treatment,* and comprehensively addresses the target outcomes described both generically in the 2014/15 Work Programme and specifically against the aims of PHC-30. EurValve is located at the nexus of this developmental area, as it deals exactly with the integration of comprehensive patient-specific data aligned to a disease-specific digital patient representation that informs a Decision-Support system to optimise the diagnosis and treatment of the predominantly-elderly heart valve disease sufferer. The table summarises the relationship to key Work Programme and Call concepts in terms of challenges and scope, developed descriptively below. Impacts are described in Section 2.

[15] Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009;373:1382–1394.
[16] Lung et al. 2003
[17] Gaemperli et al. 2012
[18] Carlsson et al.2012
[19] Mahedevia et al. 2014
[20] Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC)1; European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451-96. doi: 10.1093/eurheartj/ehs109. Epub 2012 Aug 24.

Source	Target PHC-30 Features	EurValve Implementation
Work Programme	Active, Healthy ageing	Heart valve disease is a condition of the elderly
	Disease burden	13% of elderly population (over 75) have heart valve disease
	Economic fallout	annual market affected by EurValve totals at least €4.5 Billion, see section 2.1.3
	Clinical translation	Simple DSS is already in use; upgraded version will ensue
	Improved outcomes	Unquestionably the target
	Reduced inequality	Enables all centres to be as good as the best
	Understanding health	*In silico* models represent all known and computed parameters
	Sustainability	Standardised model representation can be easily updated
	Data exploitation	The first comprehensive use and re-use of all HVD domain data in a model-based approach to physiological assessment
	Prevention, diagnosis, treatment, management	Certainly diagnosis, treatment and management
	Health monitoring	DSS output can be constantly updated with new image data
	New healthcare delivery	The first (of many…) multifactorial *in silico* systems
	Supporting enterprise	Sophisticated extension to SME product range; exportable
PHC-30 Challenges	Existing digital personalised models, tools, standards	Exploits existing curated models from CellML repository
	Integrated patient information	Will define the context-specific 'digital patient' for valve disease
	Multiscale, multilevel	Operates from cellular to whole-organ
	Current and historic patient-specific data	Patient history, updated with all available current measures
	Population-specific data	Personal data is supplemented by population-matched data
	Integrated (digital patient) representation	Inherent use of domain-specific patient avatar
	Knowledge extraction	Machine learning approach automates knowledge creation
	Decision Support	DSS is the primary focus of the project
PHC-30 Scope	Heterogeneous data	The target is maximal use of all available patient data
	Subject-specific computer models	*In silico* techniques ensure individualised representations
	Integrated data analysis	Algorithmic decision support operating on *in silico* simulations
	Highly-visual data representation	DSS is extremely visual and intuitively user-friendly
	Friendly interactive exploratory interface	DSS is extremely visual and intuitively user-friendly
	Assured acceptability by healthcare professionals	Builds on existing successful commercial CE-marked DSS product
	Personalised predict/decision: prevent/diag/treat	Solidly aimed at contributing to all these clinical objectives
	Data protection and ethical considerations	See section 5.1
	Inherent uncertainties and limits of prediction.	Assessment of uncertainty is a specific task in EurValve
	Models already available, multi-level, multi-scale	Uses multiscale systems developed in FP7 euHeart project
	Integrated with individual and population data…	Comprehensive data use, with population data when needed
	• Molecular, cellular genomics and epi-genomics • Imaging, therapeutics, nutrition and environment • Link to personal physiology, disease models	} EurValve Digital Patient includes image, proteomic, EHR } and activity data to personalise a model to characterise the } pathophysiology of the individual
	Personal medical data accumulated over time.	Full patient record is used within the DSS models
	Integration of data from other new technologies	Environmental and activity data from 'wearables'
	Gender and ethical issues considered	See sections 1.4.6 and 5.1

Table 1 Relation to the Work Programme

The **specific challenge** is to develop a digital patient, specifically in the context of heart valve disease, which integrates heterogeneous patient data, complemented by population data where appropriate. The data will be interpreted by the operation of a computational model that produces new diagnostic and prognostic measures across the physiological envelope of the patient, not only under clinical measurement conditions. The model is inherently multi-scale. The anatomy of the valve is determined from medical image data, and this is represented in a three-dimensional (3D) model. The flow through the valve, and the resulting pressure gradients and physiological sequelae, are determined by the complex interaction of the heart, the valve, and the afterload presented by the circulation, as well as by predisposition associated with the genetic profile of the individual. The components of the heart and of the circulation that are not described explicitly in 3D are represented by zero-dimensional (lumped parameter, time variant) or one-dimensional models as appropriate. A major challenge is to tune these models using the heterogeneous data that is available about the patient so that they are able to evaluate the effect of the disease under a range of patient activities.

The **scope** is to develop a DSS that integrates the data with the model to improve the management of heart valve disease. The target user is the healthcare professional. A major focus will be on the development of a highly visual representation that will assist the clinician in access to, and interpretation of, the data. The system will be designed also to assist the clinician in communication with the patient, enabling the easy description of the consequences of the disease, the prognosis, and the treatment options.

The models themselves, and the computational infrastructure to operate the models, already exist. The former have been developed over many years of research by a broad research community. An important collection of **curated models**, including some that have been contributed by the current proposers, is publicly available in the CellML model repository. The infrastructure was developed in a 14.4M Euro Integrated Project, VPH-Share. The data that will be integrated into the model includes molecular data, imaging data and demographic and other information from the electronic patient record, complemented by tools for the inference of missing data based on population data.

A key concept is that the digital patient evolves over time, becoming an increasingly accurate representation of the individual, as new data is available (whether from new measurements on the patient or from new relevant population data).

1.3 Concept and Approach

1.3.1 Overall Concept

The concept underpinning the project is that of the digital patient, in which we combine all available data on a patient, and interpret it through the operation of a computational model. The outputs, novel disease characterisations and ranked intervention alternatives, are provided to the cardiologist to support their decision.

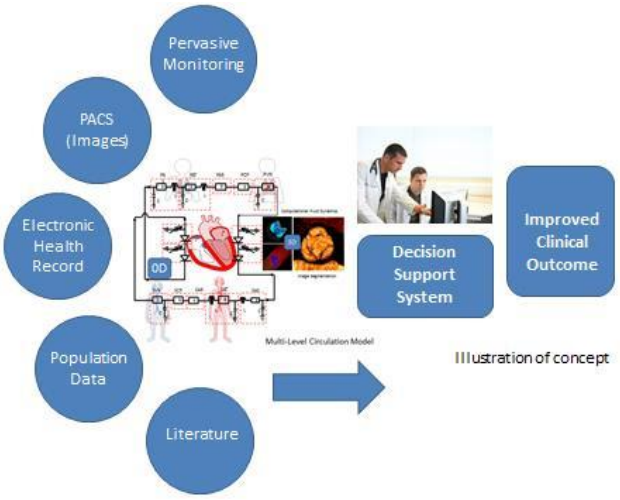

Figure 4: Model-based interpretation of heterogeneous data to provide decision support

The pathway from data to information is illustrated in figure 4. The heterogeneous data sources (Electronic Health Record data, PACS (Image) data, population data, pervasive monitoring data and literature data) all combine to inform the parameters of the model, transforming it into a representation of the individual patient. The operation of the model is controlled by the Decision Support System, which presents the output (e.g. valve pressure gradient, systemic pressure and flow distributions, clinically-relevant cardiac physiological parameters such as ventricular afterload, end diastolic volume) in a graphical and intuitive way to the clinician, resulting in a better-informed decision about treatment.

- The patient's physiological status can be described by a computer model, with two important consequences:
  - The model can provide quantitative measures that are able to characterise the physiological status and contribute to diagnosis.
  - Changes in the components of the system, or of the 'forces' on the system, are reflected in physiological changes that can be predicted by operation of the model. Thus the effects of prospective interventions can be simulated.
- It is assumed that there is an association between the physiological status and the biological response, including for example the modelling and remodelling of the heart under the loads that it generates and to which it is subjected. This biological response might be described by specific pathways and mechanistic models, and/or it might be evaluated in terms of individual propensity to particular outcomes based on population studies.

The computational models at the core of this project are a series of published compartmental models that describe the distribution of flow and pressure in the cardiovascular system, combined with anatomically accurate models based on 3D and 4D imaging of the patient. Specifically for the diagnosis of heart valve disease and for valve interventional planning it is important to be able to assess the pressure gradient across the valves, any leaks through the valves (the focus is on mitral and aortic valves) and their contribution to the loads on the chambers of heart and its effectiveness in supplying blood to the circulation. It should be emphasised that the novelty of this proposal lies not in the computational models (the partners have strong established expertise in all aspects of these models) but in the combination of these models with the heterogeneous clinical and population data.

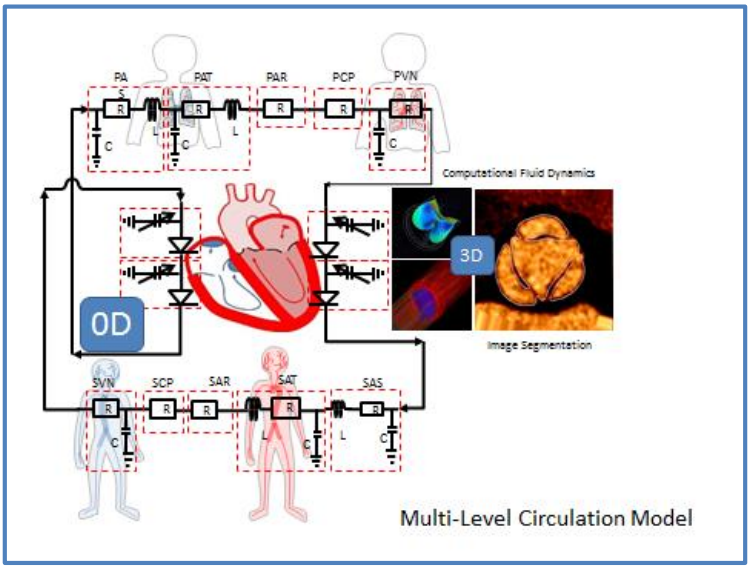

Figure 5: Multi-Level Circulation Model: All components already exist: the EurValve challenge is tuning to the individual, using all available patient data.

The components of the model are illustrated in figure 5. The model is fundamentally multi-level. The region of the valve is described in anatomical detail, based on the medical image of the patient. The circulation is described in terms of compartmental electrical analogue models that are able to represent the variations of pressure and flow throughout the system as a function of the compliance and impedance of the vessels. The figure indicates which of the anatomical elements is represented by each part. A specific implementation of the digital patient that includes all data, measured or derived, that is relevant to this patient, and to this disease process, will be developed. This type of representation is sometimes called a Reference Information Model, a key deliverable at PM3.

The concepts that will feature in this representation are hugely heterogeneous, including such diverse elements as the specific parameters in the electric analogue circulation models, the pressure and flow distributions, demographic data, proteomic data, image data, co-morbidities and lifestyle factors. Linkages between these concepts will come from literature sources and from machine-learning operations on both public and our own databases. Examples of the linkage between the parameters in the physiological model and the EHR will include: the stiffening of the vasculature with age or with co-morbidities; the association of diabetes with increased microvascular resistance; and the link between contractility and proteomics data. The result will be a level of personalisation of the physiological model that has never before been achieved. Within this overall concept we propose to include several specific and novel strands that have become possible through work in recent FP7 modelling projects, and these are outlined briefly below.

1.3.2 Technology Readiness Level

EurValve brings together a set of technologies that are now well-established within the *in silico* medicine community, and which will be combined and uniquely configured into a tailored mechanism focused on heart valve treatment optimisation. Tabulated below are the key elements being assembled, with an indication of the technology readiness level of direct relevance to EurValve.

Technology	Description	Status	TRL
Decision Support System	The complete clinical software system	CE-marked clinical system is already available for sizing for endovascular planning … but comprehensive model-based physiological decision making is not	9 2
Case-Based Reasoning	'Place my patient in a population context'	Data retrieval mechanisms well-established	6
Machine Learning	Generation of domain-specific rule sets	Well-established	6
Imaging	High-resolution anatomical imaging	Well-established in routine practice	9
Segmentation	Automated extraction of geometry	Well-established, requires tailoring	7
Systems Models	Core simulation technology	Well –establshed, curated models in CellML	7
ROM	Calculation speed enhancements	Techniques established and validated	4
Sensitivity	Tool libraries available	Coding for domain required	7
Proteomics	Protein/tissue interaction	Several basic linkages already modelled	3
Clinical Data Management	Collection and sharing of data	*TrialConnect* technologies, proven integration	9
Avatar	Domain-specific parametric representation	Concept mature; domain version required	7
Personal monitoring	Automated activity monitoring	Well-established, mature	8
Infrastructure	Service execution on hybrid clouds	Fully functional in VPH-Share	7
The TRL of the EurValve DSS will develop significantly during the life of the project, ultimately reaching TRL4 with movement towards TRL5.			

Table 2 Technology Readiness Levels – Major Components

Entry to market is probably most critically affected by overall commercial experience in the Decision Support domain as, once a business framework for clinical support has been established, the first barrier to market entry has been removed. The introduction of enhanced mechanisms offering improved outcomes, whilst not necessarily without complexity, is nevertheless a challenge of a different category.

The Decision Support System that will be developed in this project represents a significant practical and philosophical advance on existing tools, as it combines powerful mechanistic modelling of patient physiology with a comprehensive level of personalisation, based on maximal information about, and relevant to, the patient; this has never before been achieved in this domain. Nevertheless, the EurValve DSS software environment will build firmly on a basic core DSS engine that is already commercially available from industrial partner Therenva, and on already-deployed added-value clinical information modules provided within current imaging workstations manufactured by partner PHILIPS. As a consequence the EurValve system can be expected to develop rapidly towards clinical application. These existing technologies are discussed next.

Therenva: EndoSize

Therenva develops and markets the leading endovascular case planning software EndoSize® (CE-marked and FDA-approved), providing surgeons and cardiologists with an efficient tool for choosing the optimal procedure strategy and implant device based on patient CT images. EndoSize enables Physicians and Clinical Specialists to select patient CT scan studies from various DICOM data sources, view them, and process the images thanks to a comprehensive set of tools. EndoSize is intended to provide a clinical decision support system during the preoperative planning of endovascular interventions such as the selection of the endoprosthesis and the best interventional approach. EndoSize currently contains five modules dedicated to each type of endovascular intervention (EVAR, TEVAR, FEVAR, TAVI or peripheral stenting).

The TAVI module is composed of 4 steps: aorta artery segmentation, valve plane placement, measurements, report generation. Three main access routes are currently considered: the femoral artery, the subclavian artery and the apex of the heart. Individual selection of an access is based on patient anatomy, cardiac anatomy and cardiovascular disease. The user is guided through the choice of the best therapeutic strategy. The segmentation of the arteries simplifies anatomical measurements along the vessel centrelines. The physicians can visualise a simple representation of the endoprosthesis on the patient scan in 3D and they are automatically warned if the selected endoprosthesis is inadequate. The report generates the proper sizing worksheet and makes pictures ready to print or send. Video can be easily added for clinical case presentation. EndoSize records the sizing process and manages patient data follow-up for rigorous traceability.

PHILIPS: ISP TAVI

PHILIPS offers several products related to the diagnosis and treatment of valvular disease. One example is a package for the quantification of mitral valve structures in cardioechographic images. Two further products support transcatheter aortic valve implantation (TAVI). The first one (ISP TAVI Planning package for CT) supports TAVI planning decisions and device selection. In particular, measurements are supported such as the aortic annulus diameter, aorta diameter and coronary ostia to aortic valve distance. The second product (HeartNavigator) adds to this support for the actual intervention based on a life-overlay of a 3D aortic valve model onto the x-ray image. Both TAVI-related products build upon state-of-the-art technology for the automatic segmentation of the aortic valve in CT images that has previously been built within PHILIPS and continuously been advanced over the last few years. The table below identifies relevant PHILIPS intellectual property.

#	Title	Relevance
WO2011132131A1	Diameter measurements in their anatomical context	Accurate image analysis
WO2012063204A1	Identifying Individual Sub-Regions of the Cardiovascular System for calcium scoring	Region-of-interest identification
WO2014195237A1	Analysis of Mitral Valve Motion in 4D TEE for TAVI Planning	Dynamic imaging capture
US20130231564A1	Automated three dimensional aortic root measurement and modelling	Precision identification in 3D

Table 3 Philips' Relevant Intellectual Property

1.3.3 National and International Context

The physiological models and computational infrastructure that underpin this project have been developed in the Virtual Physiological Human initiative, which received approximately €260M of EC funding in FP7. The challenge in EurValve is the integration of all available patient data to perform the maximally-effective personalisation that will drive the decision support 'engine', requiring optimised matching of constituent systems. The components of EurValve have been drawn carefully from the rich supply of resources developed in FP7, and an overview of the relevant projects that contribute models, tools or infrastructure directly to this project is presented in the table below together with a discussion of the national and international context of the work defined in the current proposal, and the specific anticipated contribution to EurValve.

Project Name	EurValve Partners	Fund	Period	Strategic Importance	Contribution to EurValve
VPH-Share www.vph-share.eu	USFD (CO) CYFRONET (WPL) STHFT (WPL) PHILIPS TU/e	FP7 14.4M€	2011 - 2015	VPH-Share is a large FP7 infrastructure development IP creating a secure cloud-based software development framework for use by the VPH community. Supports the integration of tools, models and data to create, develop and operate clinical workflows, typically to derive novel computed quantifiable biomarkers. Developed and deployed model sensitivity analysis tools.	**Domain-specific infrastructure, and aggregated tools, for efficient clinical workflow development.**
euHeart www.euheart.eu	PHILIPS (CO) USFD (WPL)	FP7 16.9M€	2008 - 2012	euHeart was the largest single Integrated Project in domain of Virtual Physiological Human. It developed models and tools for analysis of cardiac and cardiovascular systems, including heart valve application.	**Tools, models and data for cardiac analysis**
MD-Paedigree www.md-paedigree.eu	DHZB USFD	FP7 11.8 M€	2013 - 2017	MD-Paedigree is a clinically-driven VPH project that validates and brings to maturity patient-specific computer-based predictive models of various paediatric diseases, thus increasing their potential acceptance in the clinical and biomedical research environment by making them readily available not only in the form of sustainable models and simulations, but also as newly-defined workflows for personalised predictive medicine at the point of care.	**State-of-the-Art approaches to interoperability**
Cardioproof www.cardioproof.eu	DHZB	FP7 4 M€	2013-2016	Cardioproof is a proof-of-concept project evaluating the comparative clinical efficacy of model-driven decision support tools vs. conventional diagnostic and treatment algorithms. It is an exemplar for the EurValve project process, as it: • Consolidates the outcomes of previous VPH projects, • Checks the applicability and effectiveness of predictive modelling and simulation tools and • Validates them in interrelated clinical trials in European centres of excellence Several cardiac models and interventional tools have already been clinically validated by clinical partner DHZB within Cardioproof, as has clinical trial infrastructure technology TrialConnect.	**Methodology for utilising existing project outputs; prove models.** **Trial data infrastructure**
E:med Systems Medicine project (SMART) http://www.bmbf.de/de/6942.php	DHZB	German 3.4 M€		E:Med is a research concept that promotes systems-oriented research into diseases and preventive measures by linking life sciences with information sciences. SMART is establishing individualised strategies for the prevention and management of heart failure by early detection of the physiological, genomic, proteomic and hemodynamic mechanisms that lead from one common cause of ventricular dysfunction (pressure overload) to maladaptive remodelling and irreversible HF. Interrelates models describing genome, proteome and cell function, regulating hormones, tissue composition and haemodynamic whole organ function	**Systems integration and linkage between disciplines** **Orchestration of multiple models in the cardiac domain**
ARCH	TU/e PHILIPS	FP7 3.8M€	2008 - 2012	Project developed computational infrastructure for surgical decision support including sensitivity and uncertainty analysis tools	**Integration of sensitivity tools with simulation systems**
MeDDiCA	USFD (CO) TU/e	FP7 1M€		Project educating researchers in the field of cardiovascular medical devices and contributing to enhanced knowledge and skills in the field of cardiovascular health care	**Training, communications and exploitation**
PL-Grid	CYFRONET (CO)	Polish 68 M€	2009 - 2015	Managed by CYFRONET, the PL-Grid programme is a series of four Polish projects establishing a stable, reliable, powerful and secure computational science infrastructure. It also supports development and deployment of specialised tools for personalised medicine and biology.	**Bedrock technology capability in secure infrastructures**

Project Name	EurValve Partners	Fund	Period	Strategic Importance	Contribution to EurValve
MAPPER	CYFRONET (WPL)	FP7 2.4 M€	2010-2013	MAPPER deployed a computational science environment for distributed multi-scale computing and included cardiovascular work on in-stent restenosis. Core distributed computing infrastructure which will be used as a basis for developing the infrastructure support for coupling computational models in EurValve	**Approaches to coupled multiscale model interaction**
UrbanFlood	CYFRONET (WPL)	FP7 2.9 M€	2009-2012	Internet-based hosting platform for Early Warning Systems validated in urban decision support environment. Used distributed computing infrastructures and virtualised resources from clouds. The concept of Common Information Space allows integrating distributed components of decision support systems and will be reused in infrastructure layer of the EurValve project	**Fully operational cloud infrastructure of direct applicability to EurValve**
SPHERE	UBRIS (CO)	16.9M€	2013-2018	Large UK national health technology project, developing sensors and data fusion technologies for pervasive monitoring of lifestyle and activity. Includes data-fusion and data-mining capabilities to make sense of data and disaggregate inappropriately common data signatures. The project spans ultra-low-power energy-harvesting wearables, 3D video analytics, environmental sensors and machine learning. Strongly practical, the project has already deployed devices in a dedicated experimental house, conducting a formal clinical trial (weight gain in pregnancy – 'ALSPAC')	**Activity monitoring, data fusion, wearable devices. Practical facilities**
NRW Initiative	PHILIPS	German 4.6 M€	2007-2013	Improving trans-catheter delivery of aortic valves: Development of a percutaneous transluminal implantable prostheses, and an implantation guidance method using multiple imaging modalities The project developed an improved valve prostheses and investigated a new guidance mechanism for transcatheter aortic valve implantation using multiple, complementary imaging modalities (US, X-ray, CT, MR). Required the generation of patient-specific heart and aortic valve models from images and approaches for fusion imaging that exploited patient-specific heart and aortic valve models.	**High-resolution multimodal cardiac imaging** **Image fusion** **Patient-specific cardiac models**
ITEA 2 Mediate	PHILIPS Therenva UR1	EUREKA	2011-2013	Mediate (ITEA2, 2011-2013). The objective was to support the healthcare professionals in the transition from invasive open surgery to minimal invasive. The technical focus was on image guided intervention and treatment by integration in the intervention room of image/data sources, displays and device actuators	**Image and Data Integration** **Visualisation**
HeartCycle	PHILIPS	FP7 21.6 M€	2007-2013	HeartCycle (grant agreement n° FP7-216695) was an EC Integrated Project coordinated by PHILIPS. HeartCycle aimed at the development of a closed-loop disease management solution being able to serve both Heart Failure patients and Coronary Heart Disease patients, including hypertension, diabetes and arrhythmias as possible co-morbidities. The HeartCycle approach is to close the loop between patients and professionals, giving appropriate access to monitoring, diagnosis and treatment results and reacting immediately, adapting personalised care plans and using automated decision support to derive therapy recommendations.	**Automated decision support with care plan optimisation** **Integration of systems across multiple related clinical pathways**

Table 4 Pertinent European Research Involving EurValve Partners

1.3.4 Overall Approach and Methodology

The EurValve project is a logical sequence of four overlapping product-related activities in which - against a backdrop of secure data storage (WP2) - a set of data processing and modelling tools is assembled (WP3), the digital patient definition is created and employed (WP4), the novel clinical decision support system is developed (WP5), and the resulting system is evaluated on a patient cohort (WP6). The project's parallel exploitation strand (WP7) ensures that the opportunities for the resulting integrated system are maximised. The basic guide shown below is elaborated considerably in Section 3.

WP	Activity Phases ->	Specify	Assemble	Integrate	Trial	Evaluate
WP2	Preparation of a secure data storage facility					
WP3	Development of a unified data-processing tool set					
WP4	Definition and use of the Digital Patient					
WP5	Development of the CDSS					
WP6	Clinical evaluation					
WP7	Exploitation					

Table 5 Workpackage structure and phasing

Aspects of the project's activities are explored in more detail in the sections below, beginning with a discussion of the clinical conditions that are the target of the development.

1.3.5 Project Key Phases

The project is organised into five phases, outlined below. Overlap between phases allows for the start of later elements before completion of every aspect of the previous phase. The overall strategy is to release stand-alone tools and components at the earliest opportunity, so that the integration can take place on fixed and formal releases. The Decision Support System releases occur later than the toolkit releases for the same reason.

#	Phase	PM	Purpose	Components	
1	Specification	01–06	Specification of all the components of the project and their interactions	• Digital patient definition • Data warehouse and schema • Software components specifications	• Infrastructure specification • Clinical inclusion criteria • DSS specification, including case-based reasoning
2	Assembly	03-15	Creation of components	• Tool and infrastructure development	• Data entry • External knowledge assembly
3	Augmentation & Integration	15-28	Integration into DSS	• Data entry, inference, new measures • Machine Learning	• Interpretation • Beta release • Case-based reasoning
4	Candidate S/W	18-30	Exercising on data	• Toolkit refinement	• Data report
5	Summary and Evaluation	31-36	Updates, eval'tion and reporting	• DSS candidate release • Evaluation at clinical centres	• Support and technical evaluation

Table 6 Project Phases

1.3.6 Gender Analysis

In aortic valve disease, gender specific differences in the progression and regression of morphological, molecular and gene expression changes due to ventricular pressure overload in aortic valve stenosis have been reported[21]. In brief, women and men appear to have a different genomic response with better metabolic adaptation in women and more myocardial fibrosis and dilatation in men[22]. At morphological level, more adaptive remodelling was found in women and more maladaptive remodelling in men. In women, maladaptive remodelling occurred less frequently than in men but was associated with impaired survival[23]). This is well in agreement with data we obtained in rodent models for pressure overload and cell systems[2425]. Furthermore, sex specific morphological and genomic predictors of contractile function in the human heart have been identified. Oestrogen led to sex-specific genomic responses in the human heart and in isolated mouse myocytes[26].

[21] Previous work of DHZB
[22] Petrov G. Circulation 2010
[23] Petrov, Abstract AHA 2013, accepted
[24] Fliegner, A J Physiol, 2010
[25] Dworatzek, CVR 2010
[26] Kararigas, JaCC 2010

Nevertheless, even in the subgroups of women and men, it remains poorly under-stood why some individuals develop only a modest and compensated form of cardiac dysfunction or present with reverse remodelling after intervention whereas others (with same aetiology) have a rapid transition into a decompensated irreversible state of heart failure and/or present with adverse remodelling after intervention.

For a better understanding of these processes, the first large-scale reconstruction of the metabolic network of the human cardiomyocyte comprising 1233 metabolic reactions and 560 transport processes in six compartments have been developed that can be applied to disease stages[27] to explain these interactions between gender, cell metabolism and cell function on an individualised basis. Along this line, we currently are in the beginning to understand parts of the complex interaction of personal risk factors with disease-accelerating circumstances which leads to a complex gene and protein signature promoting the typical features of HF like cardiac hypertrophy, systolic and diastolic dysfunction, impaired hemodynamic, cardiac fibrosis and inflammation as well as impaired electrical remodelling.

1.4 Ambition

1.4.1 Beyond the State of the Art - Introduction

The Decision Support System developed in EurValve represents a significant advance on current practice, because it combines the power of mechanistic physiological modelling with a level of personalisation that has not hitherto been achieved. In complete alignment with the key concept of PHC-30, the emphasis is not on modelling innovation – the necessary models already exist; the advances lie in the development of the digital patient (the 'patient avatar' that encapsulates all relevant information about the patient) and transforms this, through a computational model, into an effective diagnostic and interventional planning tool, and in the orchestration of multiple additional practical technological platforms that combine to provide a seamless, clinically-compliant system. Tabulated here are the 5 key technologies (grouped from the TRL analysis earlier), which are then detailed in the text following.

#	Group	Technology	Description	Innovation Summary
1	Decision Support	Decision Support System	The complete clinical software system	Maximal data; *in silico* simulation
		Case-Based Reasoning	'Place my patient in a population context'	Clinically-rich specific support
		Machine Learning (T3.1)	Generation of domain-specific rule sets	Optimised novel rule sets
2	Modelling	Segmentation (T3.2)	Automated extraction of geometry	Exquisitely matched to VHD
		Systems Models (T3.3)	Core simulation technology	Optimised mix of working models
		Sensitivity (T3.4)	Tool libraries available	Latest toolkit, customised for VHD
		Proteomics (T3.5)	Protein/tissue interactions	First linkage of twin approaches
		ROM (T3.6)	Calculation speed enhancements	Very latest high-speed approaches
3	Avatar	Avatar	Domain-specific parametric representation	Uniquely structured descriptors
4	Activity	Environmental monitoring	Automated activity monitoring	Novel use of activity monitors
5	Computing	Infrastructure; Data Management	Infrastructure; collection & sharing of data	Cutting-edge Cloud facilities

Table 7 Key Technologies

1.4.2 Technology #1: Decision Support in Medical Science

Decision support systems are becoming indispensable in medical research and clinical practice. The goal is to enhance the inference process which can lead to both diagnosis and treatment formulation. Effectiveness has been the focus of recent studies: Moja et al[28] claim that a statistically significant effect was evident in the prevention of morbidity among a study group of over 13,000 patients, while Kawamoto[29] reported improved practitioner performance in 64% of cases. DSS systems also have the potential to streamline patient care, reducing costs.
DSS systems can be categorised as **knowledge-based** and **non-knowledge-based**[30]. In the former the system comprises a knowledge base plus an inference engine and user interfaces and decisions are made on the basis of expert knowledge. In the latter, no knowledge base is present and the system relies instead on machine learning algorithms to infer knowledge from past cases.

Two sectors of healthcare in which such systems have successfully entered the market are pharmacy and billing.

- In **Pharmacy**, computerised systems screen for drug contraindications (e.g. ViroLab, by CYFRONET et al)

[27] Karlstädt, BMC Systems Biol. 2011
[28] Moja L, Kwag KH, Lytras T, Bertizzolo L, Brandt L, Pecoraro V, Rigon G, Vaona A, Ruggiero F, Mangia M, Iorio A, Kunnamo I, Bonovas S, "Effectiveness of computerized decision support systems linked to electronic health records: a systematic review and meta-analysis", Am J Public Health. 2014 Dec; 104(12):e12-22. doi: 10.2105/AJPH.2014.302164. Epub 2014 Oct 16.
[29] [2] Kawamoto K, Houlihan CA, Balas EA, Lobach DF. "Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success." BMJ 330 (7494): 765. doi:10.1136/bmj.38398.500764.8F.
[30] [3] Berner ES, ed. Clinical Decision Support Systems. New York, NY: Springer, 2007.

- In **Billing**, computerised systems examine treatment plans and suggest cost optimisations.

A key obstacle has been workflow integration: a lack of standards has hindered interoperability. In clinical settings it is common for medical practitioners to copy manually the data into a DSS, then manually transfer the results back. So additional mechanisms to integrate external systems are required[31], and are a EurValve focus.

The medical domain introduces some specific restrictions when dealing with distributed systems. These apply chiefly to security and confidentiality of medical data. In less security-minded domains of science, public cloud computing platforms have enjoyed considerable success as the base technology driving computationally-intensive research. Cloud infrastructure providers are attempting to bridge this gap by demonstrating that data can indeed be stored and processed securely in a public infrastructure – for example, the Microsoft Azure cloud is claimed to comply with the EU Data Protection Directive (95/46/EC) as well as with the corresponding US legislation. This creates the possibility of deploying DSS workflow components outside the confines of medical institutions (which are often poorly equipped to cope with the maintenance tasks involved in operating computational infrastructures) and instead provide such components in a SaaS (Software-as-a-Service) scenario. Based on our experience in the VPH-Share project, we therefore propose a platform that will:

- Manage clinical workflow computational/data services, particularly those from THERENVA and PHILIPS;
- Plan for execution of a clinical workflow to minimise the related costs, and deliver results quickly;
- Maintain security and confidentiality throughout the workflow execution process.

Our platform will facilitate interaction on defined security levels with external components equipped with APIs (including computational services and databases), and will support deployment of DSS workflows in flexible execution containers, enabling installation in arbitrary computing infrastructures, including bought-in resources.

1.4.3 Technology #2: Modelling Technologies

Modelling offers a unique approach to the exploration of interactions that are otherwise not accessible to conventional experimental investigations. Chronic pressure-volume overload leads to myocardial hypertrophy and if left untreated to end organ damage and ultimately to heart failure and death[32]. However, the reasons why some individuals develop only a modest and compensated form of cardiac dysfunction - whereas others (with the same aetiology) have a fast transition into a decompensated irreversible state of heart failure - remain poorly understood. The onset and course of heart failure is triggered by multifactorial mechanisms that are part of a complex regulation network influenced by intrinsic factors (genes, hormones like mineralocorticoids), “personal“ risk and life-style factors (like obesity or environmental factors influencing epigenetics) as well as a multitude of modification factors such as the immune system, and associated diseases (hypertension, renal disease, diabetes). Changes in gross anatomy or haemodynamics (e.g. from valve disease) can induce pathology at the cellular-tissue level. EurValve will integrate available modelling technologies to address these issues, and in doing so will innovate significantly, detailed below under six subheadings corresponding to the technical tasks in WP3.

1.4.3.1 Machine Learning (Task T3.1)

Machine learning has already been used for supporting diagnosis of heart valve disease, as in Inbarani et al[33] and Maglogliannis et al[34], but for this proposal it is not appropriate to use only data and machine learning algorithms, some form of knowledge needs to be added; we therefore use knowledge embodied in computational mechanistic models of physiology, with various degrees of sophistication. Input parameters of these models are needed, in particular relating to contractility, passive stiffness and blood flow, allowing derivation of information important to decisions on interventions, including trans-valve pressure gradients and the work the heart must do. We seek to use learning to derive values for such parameters, to allow us to use existing computational models, and we will personalise the results by using patient specific data for developing learning algorithms. The process will be generic, and will be applicable to more complex mechanistic models. Challenges include the integration of learning with mechanistic models and existing clinical knowledge, the large range of parameters involved, and the heterogeneity of the patient specific and population data.

[31] Das M, Eichner J. (2010), Challenges and Barriers to Clinical Decision Support Design and Implementation Experienced in the Agency for Healthcare Research and Quality CDS Demonstrations. AHQR Publication No. 10-0064-EF Agency for Healthcare Research and Quality.
[32] McMurray et al. 2012
[33] H.H. Inbarani et al., Soft rough sets for heart valve disease diagnosis, Advanced Machine Learning Technologies Applications, Communications in Computer and Communication Science, 488 (2014), 347 – 356.
[34] I. Maglogliannis et al., Support vector machine based classification of heart valve disease using heart sounds, Computer Methods and Programs in Biomedicine, 95 (2009), 47-61.

We will use already-available rich clinical data with new data collected by EurValve clinical centres. Computational optimisation with mechanistic models will derive values of parameters needed as inputs across the patients' full physiological envelopes, to build predictive description of heart load, and machine learning will reproduce the model values derived in this way. We will also use rich data to optimise relevant parameter values with respect to the goal of better interventional outcomes. We will use data accumulated to determine missing data where necessary. These procedures will not only learn from patient data but also on information in the literature.

To investigate the use of machine learning techniques to determine model parameters for patient predictions, we will develop interpretable machine learning models and will explore ensemble techniques, in particular tree-based approaches. We will also explore the use of similarity measures to determine model parameters required for predictions. To increase the possibilities for learning we will explore directly available data and additional features that can be derived from these data using both statistical and signal processing techniques, together with strengthening algorithms by using knowledge, e,g, on heart valve disease and interventions. We will systematically use validation procedures to ensure applicability of our algorithms to new data. The learning procedures will be optimised for outcomes by exploring the use of multiple imputation.

This project will also develop a **Case-Based Reasoning** (CBR) module to provide users with quick access to typical prior situations. Synergies with the work on learning include in particular the use of expert knowledge and the use of similarity measures. The challenge is related to the variability of patients, procedures and operators, to the overload of information, and to the focus, in decision support systems, on the information itself rather than the way it is made available. For adoption the proposed solution must evolve towards a better integration of knowledge and expertise.

CBR capitalises on past experience to solve current problems, and is quite different from any other artificial intelligence problem-solving methodology in that it searches for the most specific case to reuse. Health science has been a fruitful domain for CBR[35][36][37], and among the reasons are that case histories have long been essential in training healthcare professionals, and reasoning from examples is natural for them. Aamodt and Plaza[38] describe a Case-Based reasoner as a cyclic process comprising "the 4 R's" i.e., Retrieve, Reuse, Revise and Retain. The feasibility of designing a CBR for transcatheter aortic valve implantation has been recently shown[39] but this work did not focus on investigating similarity functions and only simple representations of cases were considered. EurValve will provide clinicians with comprehensive information by using adapted visualisation and user-interfaces.

1.4.3.2 Image Processing (T3.2)

While a large number of algorithms has been developed to segment the heart chambers in CT, MR and US images, comparatively little publications addressed the segmentation of the heart valves[40],[41],[42],[43]. Often, different parts of the heart such as left ventricle and the valves are segmented separately with different algorithms and only recently integrative approaches for segmenting the heart structures together with the valves have been proposed[44],[45]. We intend to build upon these recent developments and create an integrated solution to segment the left ventricle, ascending aorta, mitral valve and aortic valve from CT and TEE images or sequences. Next to quantitative measurements such as opening area, regurgitant area or valve annulus perimeter, the approaches will be improved to accurately capture details such as calcification (for CT images) or leaflet thickness. In addition, the segmentation approaches will facilitate subsequent blood flow simulations by providing suitable interfaces to define boundary conditions and mesh models with sufficient resolution for subsequent volumetric meshing.

1.4.3.3 Personalised Image-Based and Systems Models (T3.3)

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[44] Peters et al. Comparison of CFD-based and Bernoulli-based pressure drop estimates across the aortic valve enabled by shape-constrained deformable segmentation of cardiac CT images, Proc. ISBMS 2014, LNCS 8789:211-219, 2014

[45] Weber et al. Analysis of Mitral Valve Motion in 4D Transesophageal Echocardiography for Transcatheter Aortic Valve Implantation, Proc. STACOM 2014, LNCS 8896:168-176, 2015

A comprehensive review of modelling of cardiovascular systems was recent published by Taylor *et al*[46], summarising the analysis processes and including the integration of system-level representations of the boundary conditions. EurValve requires two types of models, and the facility to couple between them:

- System models are used to compute the overall pressure and flow distributions throughout the cardiovascular system. There is a rich literature on cardiovascular systems models, summarised in two recent reviews by Shi[47] and van de Vosse[48]. Of immense value is the set of curated models that are available through the CellML (https://www.cellml.org) model repository. There are currently over 50 models of the cardiovascular circulation in this freely-accessible repository, some of which have been contributed by the partners of the EurValve proposal.

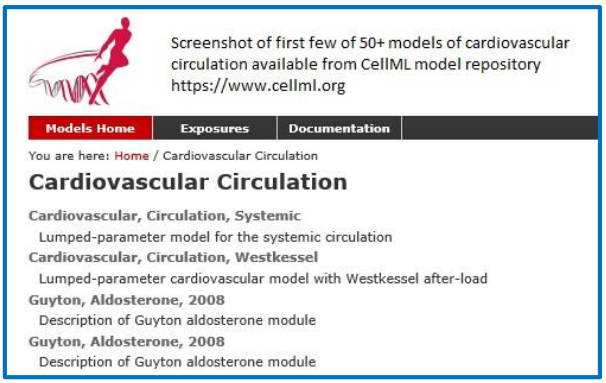

Figure 6: Cardiovascular CellML Repository

  EurValve will exploit immediately the models uploaded by USFD as part of its activity in the euHeart consortium, including the model originally published by Shi[49], which includes explicit representation of heart valve disease, and will investigate the personalisation of the Guyton models available in the CellML repository[50], including that representing the association between heart hypertrophy and pumping capacity. The modules in the Guyton model are still some of the most comprehensive available in the literature in the context of representation of the physiological processes, but we have only scratched the surface of the personalisation of these models to benefit the individual.

- Three dimensional models are used to compute the flow and pressure distributions, as well as derived variables such as wall shear stress, in anatomically accurate representations of the region of the valve of the individual patient. Several state-of-the-art examples of cardiac and cardiovascular modelling, including the modelling of diseases of the valve and of the aorta, are presented by Smith[51]. There is always a trade-off between engineering accuracy and clinical utility, and EurValve is focused on the delivery of the most effective solution process to support the clinical process. We will model the haemodynamic processes, including the compliance at the system level, but we will not use Fluid-Solid Interaction for the local 3D analyses. Two important observations from the euHeart project support this decision. Firstly it was established that the computational analysis of the valve could be greatly simplified if image data is available to provide segmentations in open and closed positions[52], with little compromise relative to a full FSI analysis, and secondly it was shown that the wave transmission effects associated with the wall elasticity could be captured, at least approximately using an efficient fluid compressibility analogue by matching of the wave speed[53].
- Coupling the models poses some technical challenges. An excellent review of the state-of-the-art in model coupling, described in the context of coronary modelling, is presented by Lee [54]. In EurValve we use system models expressed as User FORTRAN subroutines called from the commercial computational fluid dynamics (CFD) solver, with implicit coupling within the timesteps of the CFD solution. We have direct experience of the application of this approach[55]. We will also use characterisations of the haemodynamics of the valve region, based on interpolation between results of comprehensive coupled 3D models, to extrapolate to the wider physiological envelope using the 0D system modelsThe issues of model personalisation beyond image-based

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[55] Brown AG, Shi Y, Marzo A, Staicu C, Valverde I, Beerbaum P, Lawford PV, Hose DR. Accuracy vs. computational time: translating aortic simulations to the clinic. J Biomech, 45(3), 516-523, 2012.

modelling is discussed by Steinman[56]. The primary advances beyond the state of the art that will be achieved in EurValve are:

- The personalisation of the model using all of the information that is available in the clinical record and in the literature.
- The representation of the physiological envelope of the individual, extrapolating beyond the measurement condition.
- The exploration of the process of inclusion of data from the monitoring of the activity of the individual. This will exploit the rich data that is increasingly becoming available from self-monitoring of lifestyle activity

1.4.3.4 Reduced Order Modelling Tools (T3.6)

The goal of Reduced Order Modelling (ROM) is to reduce the computational complexity of 3D steady-state or transient problems. The model can then be evaluated with lower accuracy but in significantly less time. There are 3 types of ROM technique:

- ***OD Model***. Reducing a 3D problem to its equivalent electronic circuit is the most commonly used method[57]. The RLC Windkessel model describing the haemodynamics of the arterial system is a good illustration of this approach[58]. This is a simple model, but its accuracy is poor.
- ***Linear ROM***. It is possible to consider a more accurate reduced model in the linear case which is based on the modal approach. It consists in building the solution as a linear combination of the main eigenmodes of the problem. This can be used to solve steady state or transient problems[59] with the strong limitation of the linear property (linear solve and parameters which modify only the right hand side).
- ***Non Linear ROM***. The linear approach can be naturally extended to the nonlinear steady case. The eigenmodes are replaced by a more general reduced basis[60] [61]. For complex problems, a global basis could not contain major information of the system. It is necessary to build sliding local bases[62] [63]. However, in the transient nonlinear case, it is not easy to adapt the linear modal approach. A small error on initial conditions or on the full or reduced model leads to a large instability of the response for long time simulation. Building a nonlinear transient reduced model is a difficult task.

ANSYS research is focused on ROM as a technique to replace very time consuming 3D calculations by a real-time computations giving very accurate results including fields as velocities on cells. Two features have been developed:

- ***ROM for parametric studies***. First we define input parameters with variation ranges and we describe the output results including fields. In the design space represented by the Cartesian product of variation ranges we create a Design Of Experiments where we solve the 3D analysis. Then, from the solution vectors computed on these DOE points we launch Singular Value Decomposition to extract the modes, which represent the most important part of the energy. Using the projection of the solution vectors onto this set of modes we could replace a huge model by a small solve using a few equations. Finally we consider 2 steps: first we run “off-line” computations using standard solves then the “on-line” computations corresponding to any set of input parameter values are close to be real time. The ROM techniques could be applied to accurately parameterise non-linear steady and transient calculations[64].

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- ***Dynamic ROM***. A nonlinear transient solve is defined by excitations along time in boundary conditions. First we launch a full transient simulation where we store solution vectors at each time step. From this set of vectors we extract the modes. Then for any new set of time excitations on the same boundary conditions we are able to accurately calculate the full solution vector in quasi real time.

The main limitation of ROM for parametric studies is the number of input parameters we could efficiently manage. The challenging application of these ROM techniques is to accurately parameterise simulation results with respect to the human variability in terms of anatomy. An efficient technique developed by ANSYS to drastically reduce the number of input parameters representing the patient's anatomy is statistical shape modelling based on singular value decomposition in order to extract the most important anatomy modes [9].

1.4.3.5 Variation and Sensitivity Analysis (T3.5)

To use computational models for intervention planning, the models must be adapted to patient-specific conditions (personalisation) and the uncertainty in the simulated outcome measure (output uncertainty) needs to be assessed. An innovative approach, in which model personalisation is guided by sensitivity analysis and in which output uncertainty is considered, will be exploited. In this way computational modelling will be rendered useful as a tool for supporting clinical decisions.

A variance-based sensitivity analysis[65] will be applied, to assess which model parameters and boundary conditions will be most rewarding as patient-specific measures, and which others can safely be derived from the literature. This analysis apportions each fraction of the total *output* uncertainty that is due to the various *input* uncertainties, whether from a single model parameter or interactions between several, expressed by Sobol sensitivity indices. These indices can be derived analytically from a metamodel (generalised polynomial chaos expansion) that expands the model output space with multidimensional polynomials that are dependent on the input parameters, and is obtained using least square regression. To reduce dimensionality, a subset of important parameters can be identified using a screening method prior to metamodel construction. Input uncertainties will be based on measurement or population variation.

Geometry can be determined by using the routinely acquired MR protocols, while the boundary conditions can be assessed by performing MR flow measurements and blood pressure assessment.

An adaptive approach that starts with a reduced order model that will be expanded step-by-step with input that decreases output uncertainty of the prediction will be used. Considering the uncertainty of the geometry extracted from imaging data ways have to be found to parameterise the complex patient-specific geometrical shapes.

1.4.3.6 Proteomics (T3.6)

The cellular concentrations of proteins involved in excitation contraction coupling are relevant for the contractility and functionality of cardiac myocytes and also indicate changes of gene regulation during disease. In principle measured protein concentrations can be linked to function by using detailed mathematical models of excitation contraction coupling in myocytes, where model parameters are scaled by the relative abundance of proteins. We will analyse the proteome of samples obtained from patients, using isotope-labelling based quantitative methods to create deep proteomic datasets. These data will be available for the whole consortium, and will be used to explore whether personalisation based on proteomic data can yield more accurate models.

Our aim is to personalise a model of human ventricular myocytes using proteomic data. This approach goes beyond the state of the art since it combines mathematical modelling of excitation-contraction coupling with personalised proteomic data. The model will represent membrane potential dynamics with the ten-Tusscher-Panfilov-model[66][67] for human myocytes. Ca^{2+} release units will be modelled stochastically and individually[68]. A sarcomere model will simulate contraction. No sarcomere model has been specifically developed for the human cardiomyocyte based on experimental human force-calcium studies, so the approach in human cardiac electromechanics modelling studies

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[68] Schendel, T., Thul, R., Sneyd, J., and Falcke, M. (2012). How does the ryanodine receptor in the ventricular myocyte wake up: by a single or by multiple open L-type Ca^{2+} channels? European Biophysics Journal *41*, 27-39.

has been to use a phenomenological ordinary differential equation model[69]. The model[70] is designed to be readily adaptable between species, to be coupled to electrophysiological models, and is suited to be used in human heart modelling studies[71] (Nordsletten et al., 2011; Trayanova and Rice, 2011). The relative abundance of ion channel, pump, and exchanger proteins measured in proteomics data will be used to scale maximal conductances in the electrophysiological model. The feedback of troponin Ca^{2+} buffering on the Ca^{2+} transient of the electrophyiological model will be included as described in (Rice et al., 2008).

This model will serve for prediction of contractility, action potential time course and other functionally relevant cellular parameters, as well as impairment of function or tolerance to changing conditions.

These simulations will quantitatively establish the state of excitation-contraction coupling (ECC) given the patient specific expression levels of functionally relevant proteins. The detailed cell model will be embedded into the one-fibre model and will provide the patient-specific contractility.

1.4.4 Technology #3: The Avatar

The patient-specific avatar describes the integration of all acquired parameters for each individual. It includes all clinically measurable and relevant information, and also involves the derived parameters resulting from modelling processes. In conjunction, these will provide the necessary input parameters for the DSS. An exemplified list of major parameters assessed before and after valve surgery is shown in Table 8.

	Function parameters (non-exhaustive list)	Expected changes due to valve replacement/repair (non-exhaustive list)	MRI	Echo/CT	
Left ventricle (LV)	Global pump function: EDV, ESV, SV, EF	In most patients decrease of EDV Increase of EF if previously diminished	Cine MRI		**Virtual valve replacement/ repair:** **integration of all functional compartments (LV, valve, aorta, arteries**
	Myocardial deformation (elastance, myocardial contractility, PV-loops)	We expect down-left shift of the pv-loop and enhanced elastance	Tagging and computed from pressures and CineMRI	Tissue Doppler & Speckle Tracking	
	Work-load, external/internal work	Changes in external/internal work ratios will depend on afterload by compliance and resistance	Computed from 4D flow and cine MRI		
	Kinetic energy (KE) of blood	Changes in KE (less KE at systole) will depend inter alia on EDV and inflowing blood across mitral valve	4D flow		
Valve and LV outflow tract	Form, opening size	Changes depend on type of valve/surgery		Anatomy from echo (and CT)	
	Pressure gradient, regurgitation	Large reduction of gradient and regurgitation due to valve replacement/repair		Doppler echocardiography	
Aorta	Flow profiles (vortex, wall shear-stress)	Flow profiles and derived parameters will depend on type of valve device / repair technique used at surgery	4D flow		
	Compliance	Changes in compliance will be due to changes in SV, arterial pressures, resistance	CineMRI or 4D flow		
Arteries	Resistance	Changes in resistance will be due to auto-regulation, SV and pressures	Blood Pressure 4D Flow		

Table 8 Parameters to be assessed

1.4.5 Technology #4: Lifestyle and Activity Data

An entirely innovative and more speculative thread of this proposal is the integration of lifestyle into the digital representation of a patient. The particular focus is on the determination of physical activity types, the quantification of activity levels, and the resulting physiological envelope of the patient, as well as their evolution over time.

[69] Trayanova, N.A., and Rice, J.J. (2011). Cardiac Electromechanical Models: From Cell to Organ. Frontiers in Physiology *2*.
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Understanding the patient's physiological envelope and resulting load placed upon the heart in the course of a patient's daily life is important for several reasons. It is required for understanding short-term risks: an athlete places different demands on the heart to a working woman or an elderly man. It makes it possible to stratify outcomes of alternative patient management decisions in terms of active versus sedentary lifestyles. And finally, an understanding of the evolution of this envelope makes it possible to stratify outcomes by prior fitness and activity levels. EurValve will investigate the use of objectively quantified lifestyle information as an input to the DSS.

Yet, the physiological envelope cannot be reliably quantified by occasional measurements in a clinic, as it will say little about the abrupt loads or even about the average load on the heart during normal daily life, and even less about the possibly gradual evolution of the physiological envelope over an extended period of time. Thus, this aspect of the proposal leverages the technology being developed by "SPHERE" a 16ME national investment in pervasive health monitoring led by project partner UBRIS. This proposal will adapt SPHERE's ultra-low power wrist-worn activity monitor, and SPHERE's low cost Bluetooth-enabled home data hub that opportunistically downloads the activity data without user intervention. The low cost of this research system has been specifically designed for clinical trial applications.

Apart from tailoring the devices to the particular context of the project, it will also be necessary to advance algorithms that derive relevant meaning from the raw accelerometer data. This will include algorithms for activity recognition and for the computation of quantifiable metrics of activity level (intensity), specifically tailored to a set of activities of interest to clinicians. This will need to be done while taking into account the constraints of wearable devices (e.g. sample rate versus accuracy versus battery usage trade-offs).

1.4.6 Technology #5: Computational Infrastructure

Although the primary output of the project is a clinically-compliant Decision Support System, at the heart of the development process that will create it is a sophisticated information management system with important domain-specific attributes honed by partners with experience that has evolved across many years of medical infrastructure development. Significant areas of development that will extend beyond the current literature are detailed below.

1.4.6.1 Container Technologies

Operating cloud-based resources is an everyday business for current distributed applications. Although umbrella programming interfaces allow for easy integration with many available cloud providers, dynamic computational and data load migration among cloud providers is still an issue. Supporting such migrations will bring EurValve flexibility required for managing complex clinical scenarios. Also, application of lightweight containers (e.g. Docker[72], that are very small and can be run directly in the operating system, will considerably reduce waste of time (system booting time) and cost (lesser disk usage). In clinical applications, where data protection is always an issue, lightweight machine migration and execution is a necessity. They also make migration between infrastructural cloud sites less problematic. Going beyond the current state-of-the-art, within the course of the project the lightweight container technology[73][74][75][76] will be used to package and publish migrating application components that will run on various cloud resources, including standalone computers.

1.4.6.2 New Cloud Computing Solutions

Classic cloud provisioning mode assumes starting Virtual Machine and paying for it in hour based intervals. For application like DSS this can result in unnecessary waste of money, because user interaction with the application can be quite short (couple of minutes). For this type of applications it is very convenient to pay per single request, as it is possible with new services offered by cloud providers. Examples are Amazon AWS Lambda[77], Google App Script[78] and Azure WebJob[79]. This introduces possibility of novel computation policies - e.g. a biological model can be executed when new file appears in Amazon S3 storage, when a dedicated event was generated by the user, or it can be started at scheduled intervals. As a conclusion it allows to create event based infrastructure for distributed

[72] Docker: https://www.docker.com/
[73] Paid containers for Windows:http://www.boxedapp.com/
[74] http://www.cameyo.com/
[75] http://www.evalaze.de/en/evalaze-oxid/
[76] http://www.symantec.com/workspace-virtualization/
[77] http://aws.amazon.com/lambda
[78] https://developers.google.com/apps-script
[79] http://azure.microsoft.com/blog/2014/10/22/webjobs-goes-into-full-production

DSS. On the other hand, the usage of PaaS infrastructures (such as Heroku[80], Cloud Foundry[81], OpenShift[82], Google App Engine[83]) allows to scale DSS resources consumption up and down automatically, and to pay only for used resources. It allows keeping the DSS asleep (and incurring no costs) when not used and awaking it when an execution event appears.

Going beyond the state-of-the-art, in the scope of the project we will apply these innovations, and in combination with the container technologies, we will create flexible and cost effective DSS infrastructure. Operations-wise, we will also collect model execution and data storage characteristics, and we will automatically apply that knowledge to provide optimised resources allocation strategy for DSS (e.g. deciding between AWS Lambda for very short tasks and PaaS-based provisioning for more demanding cases).

1.4.6.3 Integrated Authentication, Authorisation and Accounting

Security aspects are one of the most crucial for any IT system operating on medical data. One of the security aspects is related to ensuring proper Authentication, Authorisation and Accounting mechanisms, currently supported by several possible solutions. Kerberos[8485], despite its age and complexity, is still used in many systems and provides inspiration for more light-weight system as a good example of ticket based access system. Another interesting solution is Shibboleth[86] based on SAML assertions. Its architecture is well suited for web applications and services. OpenID is an even more relaxed authentication mechanism, based on defined set of providers, which could be freely chosen from the numerous available or established on purpose. On the other hand there is no need to form closed federation between providers. The authorisation functionality needs to be provided in case of OpenID by external service either custom build or based on standard such as OAuth[87]. Finally there are numerous simple authentication systems such as plain old username and password mechanism, mutual TLS authentication using X.509 certificates or various locally generated tickets systems (such as Keystone component of the OpenStack). Those services might still be appropriate for some specific services.

The delivered solution will be outfitted with proper access control to individual elements of distributed DSS. Our goal is to provide lightweight solution which would not impact performance of the particular services (e.g., data storage access, models execution), yet on the other hand be pluggable and extendable, to permit integration with various security mechanisms described in the SotA section.

1.4.6.4 Hybrid cloud solutions

Cloud usage is very popular nowadays, but the threat of vendor lock-in still remains relevant. Every cloud provider has dedicated set of features, which are specific only for concrete site. For example when the software is integrated with Amazon cloud platform it is not trivial to migrate all elements into e.g. Rackspace, because virtualisation technology is different, data storage solutions has different API.

There are many possible ways how we can escape vendor lock trap when using cloud resources. First one is connected with using solutions which are independent of the virtualisation technique. It can be achieved by delivering dedicated installation scripts created using e.g. Chef[88], Puppet[89], Ansible[90], Salt[91], CFEngine[92]. Mentioned solutions use different languages, configuration files, but the idea is the same - user describes what need to be installed and the tool will take responsibility to do it right on concrete operating system. Unfortunately time needed to install everything from the scratch using dedicated scripts is a time consuming process. Light containers (such as Docket[93] based on LinuX Containers[94]) are and alternatives, which also allow to avoid vendor lock. It allows user to create very light container, which can be started on every machine with Docker installed. What is more it reuses libraries from the host environment, thus start of such container is very fast.

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[80] http://heroku.com
[81] http://www.cloudfoundry.org
[82] https://www.openshift.com
[83] https://cloud.google.com/appengine
[84] Kerberos: http://web.mit.edu/kerberos/
[85] G. A. Champine, D. E. Geer, Jr., and W. N. Ruh.Project Athena as a distributed computer system. IEEE Computer, 23(9):40-51, September 1990.
[86] Shibboleth: https://shibboleth.net/
[87] OAuth: http://oauth.net
[88] https://www.chef.io
[89] https://puppetlabs.com
[90] http://www.ansible.com
[91] http://www.saltstack.com/community
[92] http://cfengine.com
[93] https://www.docker.com
[94] https://linuxcontainers.org

Solutions presented above allow to deploy application into any cloud site. But sometime there is need to extend private network with the resources from the cloud. In such a situation AmazonVPN[95] is a perfect match. It gives administrator full access to network configuration (e.g. IP ranges, subnets, gateways, etc.).

Another solution which allows implementing Hybrid Cloud is a vCloud Datacenter Services[96]. It allows to migrate running virtual machines between different centres based on vCloud Datacenter. Unfortunately here we are limited only to the compute sites which use VMWare solutions. This limitation is not present for RightScale[97] solutions. It delivers abstraction above compute, storage and network resources and, as a conclusion it allows us to escape vendor lock-in problem.

1.4.6.5 Data Security

In addition to the need of proper Authentication and Authorisation services running in Cloud (especially public and hybrid one) requires high level of data security during storage and processing phases. Additionally, a mechanism that ensures that data cannot be recovered using reasonable time and resources after being deleted is also required. Multiple factors such as characteristic of some physical media (especially magnetic) as well as possible write optimisations used in modern storage systems cannot ensure that data are destroyed even when they are overwritten. Due to this fact we need to secure (e.g. encrypt) the data before storing it if permanent storage is needed. Nowadays multiple strong encryption systems exist such as AES[98]. Some situations may require usage of asymmetric system such as RSA[99] which allows to encrypt data or verify its integrity without the need to possess secret need for decryption or signing. Highly comprehensive analysis of the problem has been done in the scope of the CIRRUS project[100], including paper describing various aspects of data security and privacy[101]. It shows that problem is complex on many levels both technical and legal. Some of those aspects have been addressed by TClouds project[102] [5] which assessed legal aspects as well as created "Trustworthy Internet-scale Computing Platform" to address technical issues related to data security. Another project - SECCRIT[103] - also is focusing or legal and political aspects showing the need for complex planning from initial assessment of threats through procedures development and gaining ability to ensure accountability if something potentially would go wrong. It is also important to mention, that however not yet common, some solution exist also on the provider side. A good example is service called CloudHSM[104] (ab. from Hardware Security Module). This mechanism allows secure storage of cryptographic material protected from unauthorised access, which can be used both for in-house cryptographic solutions as well as IaaS services such as encrypted EBS or databases.

Of course the main effort needs to be focused on preventing unauthorised access to the system, however no security plan would be complete without ability to handle security incidents that might happen regardless any effort to prevent them. Part of this plan would need to take into account complex nature of Cloud Forensics, as normal methods that assume having access to real physical hardware would not apply there. Problems with good solution for the mentioned problems have been described in literature[105].

We plan to design and develop mechanism that would combine suitable well-established cryptographic standards, with key distribution mechanisms, as well as data dispersal to different zones to ensure secure storage of data in the cloud. Also we will propose mechanism to move data in and out of the cloud for the purpose of computations in a safe (private) zone. In our work we will take best practices which are outcome of the mentioned projects and choose the best way to integrate and extend them for the need of the project.

1.4.6.6 Real-time Multiscale Visualisation

Reliable visualisation working on-demand is one of the most important components of a computer-aided medical DSS. Having a graphical insight into simulated phenomena can greatly influence the decision making process.

Application delivery through web browsers has not been common for highly interactive and 3D software. Local software instances directly accessing the rendering hardware were preferred. With the introduction of the

[95] Amazon Virtual Priviate Network, http://aws.amazon.com/vpc
[96] vCloud Datacenter Services, http://www.vmware.com/pl/cloud-computing/service-providers/vcloud-datacenter-services/vcloud-datacenter-services
[97] Rightscale Multi-Cloud Platform http://www.rightscale.com/solutions/problems-we-solve/hybrid-cloud
[98] FIPS 197: Announcing the ADVANCED ENCRYPTION STANDARD (AES), FIPS, 2001
[99] RFC3447: Public-Key Cryptography Standards (PKCS) #1: RSA Cryptography, 2003 (available at: http://tools.ietf.org/html/rfc3447)
[100] CIRRUS Project: http://www.cirrus-project.eu/
[101] D2.3 Green Paper Final Version, CIIRRUS Project, 2015
[102] TClouds Project: http://www.tclouds-project.eu
[103] SECCRIT Project: https://www.seccrit.eu
[104] Amazon, AWS Cloud HSM: http://aws.amazon.com/cloudhsm/
[105] Ruan, K.; Carthy, J.; Kechadi, T.; Crosbie, M. (2011): Cloud forensics. Advances in Digital Forensics VII, pages 35-46. Springer

WebGL[106] technology the trend changed and with the availability of supporting technologies such as WebSocket[107] for data transmission and modelling abstraction libraries such as three.js[108] there are no more barriers to utilise the web for robust and platform independent application shipping.

Visualisation of multiscale phenomena has already been addressed by more formal[109] and practical[110] studies, however, the work focused only on static data available locally to the rendering platform. For cloud-based simulation setups data for different model scales is produced in real time and possibly on distributed resources. Collecting the data and feeding the rendering process in the browser poses a challenge. Current solutions (e.g. ParaView[111]) focus on server-side rendering and transmitting raster images to be presented to the user which decreases interactivity and introduces latency for high-resolution imaging.

The project will exploit available technologies and libraries for real-time visualisation and produce a framework for extracting visualisation data coming from multiscale simulations run on virtualised resources, transfer the data over to the rendering library in the DSS web application and provide callback capabilities for the running simulations if necessary by the decision support scenarios.

1.4.7 Clinical Data Systems

An infrastructure technology (TrialConnect, Telekom Healthcare Solutions) has been developed and successfully integrated into former and current EU projects (e.g. Cardioproof; ESOPE) or national project (e.g. SMART which is part of the German Initiative on System Medicine) . This technology allows the (pseudo-)anonymisation, upload, and web based management of medical DICOM images in conjunction with relevant clinical information into a study database. It will also include an electronic Case Report Form (eCRF).

The platform will be used for all prospective clinical study data acquired in EurValve. It will allow to access and process images using in part web-based tools providing seamless data integration into a modelling workflow (combined web image and clinical data management system). We expect its adoption in EurValve to be of value as it provides an established technology at a key infrastructural level of the clinical trial.

1.4.8 Innovation Potential

No existing system exploits the totality of the data that are measured or inferable about the individual patient, in combination with an image-based mathematical model, to offer strongly personalised, model-based decision support, in the context of heart valve disease, to the surgeon or cardiologist in a software environment that is suitable for routine operation in the clinical patient management pathway. The clinical staff engaged directly with this project are evangelical in their belief that such a system could transform patient management.

Two of the industrial partners in this project, Therenva and PHILIPS, are ideally placed to develop and to realise the innovative product that will bring about this transformation. Each of these partners has an existing DSS for the planning of endovascular valve interventions based on anatomical measurements, but with no concept of physiology. A description of the positioning and technology readiness level of these products was provided in section 1.3.2. These existing platforms are already familiar to the clinical community, already read patient image data and operate on it to provide recommendations on prosthesis sizing and positioning, and are the natural basis for extension to integrate the comprehensive and heterogeneous data that is the focus of the current project.

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2. Impact

2.1 Expected Impacts

Here we describe the wide range of significant results that will follow directly and indirectly from the introduction of the EurValve DSS.

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[106] https://www.khronos.org/webgl/
[107] https://www.websocket.org/
[108] http://threejs.org/
[109] Stolte, C.; Tang, D.; Hanrahan, P., "Multiscale visualization using data cubes," Visualization and Computer Graphics, IEEE Transactions on , vol.9, no.2, pp.176,187, April-June 2003 doi: 10.1109/TVCG.2003.1196005
[110] Debora Testi, Daniele Giunchi, Gordon Clapworthy, Stephen Aylward, Xavier Planes, and Richard Christie. 2012. New interactive visualisation of multiscale biomedical data. In ACM SIGGRAPH 2012 Posters (SIGGRAPH '12). ACM, New York, NY, USA, , Article 76 , 1 pages. DOI=10.1145/2342896.234298 7 http://doi.acm.org/10.1145/2342896.2342987
[111] http://www.paraview.org/

The principal output of the project will be a software system, which is anticipated to reach Technology Readiness Level 4 or 5 at the end of EurValve, intended to improve the lives of patients with Valvular Heart Disease. This system will bring immediate benefit to patients and, operating typically within national healthcare structures, will enable clinicians to offer optimised treatment, and will also increase the level of business experienced by the manufacturers themselves. The burden of illness is large, extending beyond the patients directly affected to reach their friends and family, their employers and colleagues and the wider social community that variously copes with the associated emotional and practical disruption. In cases of heart disease the need to identify the best treatment regime is particularly challenging, as cardiac conditions are often associated with long treatment delays and extended periods of rehabilitation; it is often difficult, particularly in VHD, to reach a decision quickly, and if the treatment is then sub-optimal, necessary revision adds significantly to the burden for all concerned.

There is a further category of healthcare industry benefit, in the form of the increased significance that attaches to the investigative machinery used to provide the decision support system input data, and to the treatment options identified by the system as the most beneficial. Medical device and pharmaceutical manufacturers within and outside the consortium can therefore expect increasing activity.

Across Europe, the ability of healthcare systems to improve the wellbeing of the population is a political, scientific and humanitarian objective that is widely recognised, and innovative initiatives that lead to measurable improvements are, rightly, well-supported. The recompense is a continuing improvement in national health metrics, indicators of advancing social conditions and increasing healthcare knowledge. EurValve will bring this benefit initially to the EU, where the development is centred, further establishing its innovation reputation.

Members of the consortium contribute not only to the principal development but create new knowledge in their own domains that has value beyond the primary utility. In the case of commercial partners this brings opportunities for increased uptake of their products, and academic partners can exploit their technical developments within the wider healthcare domain and beyond.

Scope	Impact	Measures
Patients	Patients' lives enhanced by optimised treatment. The personal cost of cardiac disease goes well beyond the physical, and is a major disruptive influence on daily life	Patient outcomes Micro-economic benefits Local societal prosperity
Indirect Users (e.g. family, social services)	The benefit to patients cascades to the clinicians responsible for the treatment and the healthcare systems in which they operate. The burden of cardiac disease nationally is immense.	Outcome performance Healthcare costs Treatment pathway design Broad societal prosperity
DSS Manufacturer	The DSS manufacturer will achieve improved market uptake for their systems, using conventional and cloud-based distribution. They will be able to translate the technology to additional products, services and domains	Installations count, earnings Pay-per-use earnings Staffing Additional developments Additional domains
Indirect manufacturers	Investigative and interventional device and pharmaceutical manufacturers associated with emerging successful treatments will be boosted by increased market share	Increased installations, usage Support for fresh innovation Establishment of a trade focus
Society (EU, national)	Beyond the practical societal benefit there is a major significance to elevated international standing	International disease statistics Healthcare technologies
Consortium: Commercial	The DSS is the principal but not the only output. Three consortium members will offer project-based analytical tools and additional services	Number of exploiting members New products New services
Consortium: Academic	The academic partners have additional goals to develop their domain expertise and generate new publications, beyond the State-of-the-Art	Novel research pathways Publications, conferences… Domain leadership

Table 9: Summary of EurValve Impacts

The full landscape is elaborated in the following sections:

- Section 2.1.1 focuses on the expected strategic impact at the higher health, RTD and industry policy level and also concisely explores the impact of EurValve on the objectives and challenges as outlined in the Work Programme
- Sections 2.1.2 onwards then discuss key aspects of project impact as seen from the more targeted perspectives of Europe, Industry, and the Clinic, before examining the specific PHC-30 impacts discussed in the Work Programme and how account is being taken of other RTD activities.
- Dissemination, exploitation, technology effectiveness evaluation and IPR management are considered in the following major section 2.2 on maximisation measures.

2.1.1 Strategic Impact

The EC's 2013 report 'Investing in Health'[112] brutally examines the significance of healthcare **from an economic standpoint**, but perhaps cynically makes two key points of social importance:

- Health is a value in itself. It is also a precondition for economic prosperity. People's health influences economic outcomes in terms of productivity, labour supply, human capital and public spending
- Health expenditure is recognised as growth-friendly expenditure. Cost-effective and efficient health expenditure can increase the quantity and the productivity of labour by increasing healthy life expectancy.

But there is a sting in the tail:

- The relatively large share of healthcare spending in total government expenditure, combined with the need for budgetary consolidation across the EU, requires more efficiency and cost-effectiveness to ensure the sustainability of current health system models.

We argue that *in silico* methods are **precisely aligned** with this economic drive for more efficient healthcare, and this is not at odds with patient interests; on the contrary, the inherent optimisation achieves these goals, exemplified by EurValve:

- Suboptimal treatment fails at all levels, nationally, systemically and personally for the patient. The mantra must be 'optimised treatment' if we are to extract the best value from the entire healthcare 'mechanism'. EurValve exemplifies optimisation, seeking to extract every possible nuance from the rich patient data that it employs.
- Maximally-driven treatment supports clinicians in their quest to achieve the best outcome for their patients. Healthcare systems' in-built tendency to underperform must be replaced by optimised excellence, as is hard-wired into EurValve.
- Healthcare systems also struggle to manage their data, whereas the *in silico* community supports completely the EC's policy, reiterated in the 'Public Sector amendment' Directive 2013/37/EU, for facilitating the re-use of public sector information across the EU, removing unnecessary barriers. DSS systems operate most effectively with free access to patient information, and the proliferation of effective maximal-data DSS systems will encourage the move towards systematic data reusability. This has repercussions well beyond cardiac care.

EurValve's vision of the European and global relevance and impact of the CDSS to be established is fully aligned with the two important visions behind the H2020 support for **continuing developments in *in silico* medicine**:

- The original vision of the FP7 'Virtual Physiological Human Initiative' as expressed in the STEP roadmap: EurValve will 'have impact on the way health knowledge is formalised, acquired, understood, represented, analysed, communicated and validated. It will create a new basis for healthcare and will open up new opportunities for industrial development'.
- The ambition for the H2020 Societal Challenge 1, 'Health, Demographic Change and Wellbeing' to 'supporting the translation of findings into the clinic and other health and care settings to improve health outcomes, reduce health inequalities and to promote active and healthy ageing'.

Achieving these impacts will be determined to a considerable extent by a successful RTD process, supported by a well-coordinated and managed project with respect to scientific, technical, exploitation and administrative issues. The risks to be faced and assumptions made in this context to realise the expected impacts are examined in this proposal's section on risk management.

In line with its overriding goals, EurValve's results will have a particularly high impact on this key focus of translating *in silico* technologies into the clinic, and with the project's chosen approach of updating an existing commercially-available Clinical Decision Support System we aim to maximise our chances of rapid and significant clinical penetration, minimising acceptance risk.

2.1.2 Clinical and Societal Impact

Ultimately the overriding clinical, societal and probably economic impact of this initial demonstration of clinical utility will be dramatic. The room for improving efficiency, productivity and prediction (and thereby prevention) is evident: the individual, health system and societal costs of diseases, particularly those inflicting large sections of the population, are well known, as are their impacts on the quality of life for patients and their relatives and friends.

[112] http://ec.europa.eu/health/strategy/policy/index_en.htm

Summarised here is the clinical/social cascade of benefits that follow from improved performance:

Domain	Topic	Consequent Benefit
Clinical	More effective clinical decisions due to DSS recommendations	• Increased success rate, from awareness of alternatives, risks
Clinical	Consequent reduced clinician hesitation, higher confidence in success	• Shorter operation time (10%) • Reduced risk of infection • Reduced risk of complication • Lower mortality (estimate 4%-6%)
Societal	Reduced risk of complications	• Improved patient comfort, family confidence • Reduced length of stay, minimised recovery period

Societal	Reduced hospital length of staying stay	• Reduced costs:
		  ○ Direct (hospital and medical)
		  ○ Indirect (productivity of the patient during recovery period)
		• Reduced health care insurance costs
		• Potential savings in excess of 50% (Therenva estimate)

Clinical	Increasing acceptance of simulation to minimise clinical uncertainty	• This approach is expected to revolutionise the medical world in by changing the paradigm of treatment, increasing confidence
Patient (Crossover)	• Enhanced patient confidence (motivational factor in elderly patients) • Systems as demonstrators to patients • Quotable reduced mortality inspires confidence • DSS recommendations reduces hospitalisation	• Lower pre-operative stress • Improved comfort • Maximised success rate - especially for elderly • Confidence from knowledge, technology • Hospital stays could be reduced by 30% (Therenva estimate)

Healthcare Systems (Clinical)	Truly significant impact on health care systems, structures and costs	• Productivity of surgeons will be significantly improved
		  ○ Operative unknowns are almost eliminated
		  ○ Lack of uncertainty reduces risk, clinician stress
		Therenva estimate for improved productivity: 15%

Table 10: Clinical/Social Cascade of Benefits

2.1.3 Economic Impact

Facilitation and encouragement of the optimised use of available clinical data remains a key challenge for *in silico* practitioners, and this goal is tackled comprehensively in EurValve. The central ambition is to identify and employ the fullest possible range of clinical and environmental patient-specific and population data, to bring the most complete analysis to the examination of Valvular Heart Disease. The impact of optimisation will be significant:

- In 2013 Osnabrugge et al[113] reported on the prevalence of AS, concluding there were 190,000 TAVI candidates in Europe, growing by 18,000 annually. The figures for conventional surgery were four times higher.
- The team reported separately[114] the cost of valve replacement varying from €33k to €41k.
- The annual cost of Aortic Valve replacement in the EU therefore exceeds €3.1 Billion. Mitral valve replacement rate is a little over half that for AV, so **the annual market affected by EurValve totals at least €4.5 Billion.**
- There is a huge disparity in the availability of recent treatments to EU citizens with, for example, Germany reporting[115] a fourteen-fold higher use of TAVI than Portugal.

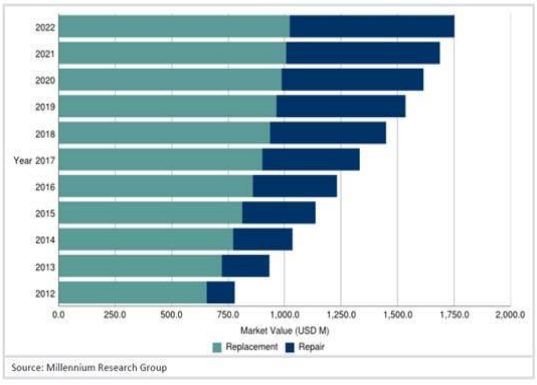

Figure 7: Growth projections for the valve market

Technology will once again be the great leveller, and EurValve will contribute to paving the way: with EurValve available via the cloud to every hospital in Europe, best practice recommendations will be instantly available to all, and in principle all citizens will share the same optimised treatment potential.

A change of just 10% in the treatment selection involves around €500M, yet **the societal impact will be even greater**; we are moving towards the greatest change in clinical practice ever, as DSS systems gradually extend across all of healthcare, bringing a migration of care towards a system that brings the

[113] Osnabrugge RL et al, Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013 Sep 10;62(11):1002-12

[114] Osnabrugge RL, Head SJ, Genders TS, et al. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. Ann Thorac Surg. Dec 2012;94(6):1954-1960.

[115] Mylotte D et al, Transcatheter Aortic Valve Replacement in Europe: Adoption Trends and Factors Influencing Device Utilization, J Am Coll Cardiol. 2013;62(3):210-219.

same quality of care to everyone, and accesses the latest validated research findings to maintain currency.

The wider impact due to healthcare domain-wide movement to *in silico* methods will be startling. In the UK alone the annual expenditure on the NHS is now €150 Billion[116]. 10% of this figure represents a remarkable benefit.

2.1.4 Industrial Impact

Because of the recently introduced Transcatheter Aortic Valve Implantation procedure for aortic valve treatment and upcoming transcatheter treatments for the mitral valve, diagnosis, treatment planning and interventional guidance related to valve disease and treatment gained high importance in recent years for manufacturers of imaging systems such as PHILIPS and related software applications such as those from Therenva. This is reflected by recent introductions of related products for TAVI planning & guidance and mitral valve characterisation. EurValve is perfectly aligned with this development and provides the basis for the next generation of products in this area.

The commercial companies involved in EurValve will immediately capture the attention of a new market from their involvement in the project. Benefits will cascade not only from the direct availability of VHD software systems that can be introduced to clinic, but also from further use of the underlying approach to maximal use of clinical data, and the mechanisms employed efficiently to derive and utilise the necessary sophisticated algorithms at the heart of the DS workflows, which will have direct utility in developments in associated domains. It is therefore additionally expected that the high-profile introduction of such tools in this important and well-publicised area will have a consequential effect wherever similar approaches are stimulated amongst relevant commercial developers.

The VHD software developed in EurValve and the underlying multi-level circulation model has an important property that makes the approach particularly attractive for companies. In particular, the approach facilitates companies to introduce predictive VPH simulations into products and tailor it for different applications, because comparatively simple compartment models are combined with more detailed simulations of relevant parts like the valves. Highly complex and comprehensive simulations of the entire heart are that are costly, risky and complex for a product introduction are thus avoided while the benefit of predictive VPH simulations can still be exploited.

Another key element of the VHD software and the underlying multi-level circulation model is its inherent capability to integrate clinical data with pervasive monitoring data. This capability allows building solutions across businesses like home monitoring and hospital equipment (like imaging systems), and it enables companies such as PHILIPS that are active in both areas to develop and offer new solutions and services that will outperform solutions focusing on only one aspect.

Perhaps most significantly, EurValve moves the business of Decision Support across an important boundary – bringing in silico medicine firmly into clinical practice. This impact will be the most far-reaching of all, as other clinical procedures will quickly follow. Building on the themes identified in the introduction, there are three categories of industrial user with which EurValve will be influential:

Group	Specific	Headline Impact
Consortium	Therenva	Significant uptake of stand-alone and cloud DSS licences. Increased sales, staff, research, exports, development rate
	PHILIPS	Extended provision of DSS-compliant imaging systems, modules
	ANSYS	Accelerated growth in clinical analysis uptake
External, DSS	Other Domains	Accelerated introduction due to H2020 PHC successes
External, VHD	Prosthesis (Valves)	Trend toward modern low-risk devices. Selection supported by EurValve system
External, Other	Activity monitoring	Already a growth area, rich opportunities for regulatory-approved devices

Table 11: Summary of EurValve Industrial Impacts

2.1.5 Technological Impact

The previous sections have referred to the impact when EurValve is deployed, but we can also measure the changes that occur as the technology is developed. Distinct from Industrial impact, we consider there to be an opportunity for EurValve to report internal technological impacts as the various components are assembled and the system is evaluated. We tabulate below the metrics that we will apply, tangible indications of progress, the results of which

[116] UK House of Commons standard note SN/SG/724

will be added to appropriate dissemination materials during the life of the project. These are practical measures of the functional assessment of the EurValve DSS system, which we consider indicative of the technical success of the design, and are quite distinct from those identified within the clinical impact category.

Indicator	Evaluation Method	Assessment Criteria
Number of models supported by the Model Execution Environment	Successful deployment and execution on the infrastructure	In Year 1 we plan to support 2 selected modelling technologies, in Year 2 an additional 3 more types
Number of public cloud providers supported	Evaluated by acceptance tests covering basic functionality of deployment and execution of services	At least 3 providers are required to provide resilience and fault tolerance, as well as flexibility of service selection and preventing vendor lock-in.
Number of simulations and analysis runs executed using the infrastructure	Evaluated using the logging and monitoring capabilities of the infrastructure.	In Year 1 we plan execute a medium-scale analysis of 100 runs (machine learning), in Year 2 large-scale analysis with 1000 simulations, and in Year 3 sensitivity studies on 10s of 1000s of executions. Note that this capacity supports the knowledge discovery process, but is not part of the clinical process.
Cost savings from the hybrid cloud infrastructure (compared to traditional h/ware)	Evaluated by comparing the actual costs incurred in comparison to the estimated cost of in-premise cluster	Expected cost savings of 60% thanks to the intermittent nature of research workload, which would result in average low utilisation of in-premise cluster.
Availability of the infrastructure	Evaluated by monitoring tools employed in quality assurance task	At least 99%, in accordance with the requirements of the users.

Table 12: Summary of EurValve Technological Impacts

2.1.6 Impact on Sharing and Generating Knowledge

EurValve combines the expertise and knowledge from expert groups selected both for their complementarity and for their collective enthusiasm to see the ambitions of the *in silico* medicine fraternity realised *in the clinic*.

Integrative research complements the classic reductionist approach by one approach in which organisms are seen as systems, and important pathophysiological processes are investigated in term of interactions across sub-systems, and across dimensional and temporal scales. This 'integrationism' also involves integration across the knowledge produced by the different sub-domains of biomedical research.

EurValve will assist this process of integration by demonstrating that the use of maximal data can fundamentally affect the integrity of the resulting conclusions, and this arises from three important concepts that pervade the planned DSS: total utilisation of available information, inference of missing data, and strategies for managing variation and uncertainty in the simulation processes.

As part of the development process we hope to demonstrate that any remaining barriers to the maximal exploitation of data should be removed in pursuit of patient or health system benefit, as these issues are of particular relevance when using patient-specific information for modelling. The same considerations apply to ethical issues, the relevance of which is not underestimated.

We therefore suggest that, regarding the **sharing** of knowledge, the concept is heavily bound up in the entire process of making available to clinical practice a tool that embodies the latest knowledge and expertise in the optimal treatment of disease; it epitomise the knowledge-sharing process, and interested users will be invited to participate in related activities.

And concerning the **generation** of knowledge, we expect there to be two related consequences:

- Users of the system will reach their own conclusions on the match between system performance and local experience. The system will contain a mechanism for the collection and feeding back of findings resulting from its use and, with agreement from the centres concerned, anonymised data subsets will be used to audit system operation and generate new findings.
- The DSS mechanism will be used as an exemplar both to stimulate uptake in other centres and to demonstrate the possibility of domain translation. We expect a proliferation of in silico DSS mechanisms in coming years, with EurValve as an early stimulus; consortium members expect to play significant roles in the furtherance of the technology.

Additionally, during the life of the project, we expect that the flexible infrastructure platform supporting multiple clouds and the model execution environment that enables deployment and execution of models on various infrastructures will contribute to the sharing of knowledge represented not only as data but also as the models.

Using the concepts and technical infrastructure of VPH-Share, it will be thus possible to share and reuse the models across the research community involved in preparation of components contributing to DSS.

2.1.7 Sustainability Beyond the Project

The EurValve consortium will develop an exemplar system that, although dedicated to one select domain, will have been constructed according to rational principles of re-usability, modularity and ease of maintenance. Consequently it will serve as a flagship for the general principle of model-based DSS operation, exploiting heterogeneous data across the clinical domain, and a key exploitation strand will be to ensure that this facet is widely understood.

The commercial organisations seeking to further their technologies in the marketplace will provide a strong impetus for the maintenance and continuing development of the software system, and this is discussed further under Exploitation. The significance is that by introducing from the outset discussion of the ways in which the resulting technology can continue to be developed, the EurValve consortium will avoid the pitfalls that derive from last-minute attempts to foster agreed support, and will establish a sound basis for continued platform sustainability.

An additional strand of importance to the VPH community is the planned availability of relevant EurValve components, whether open-source or licensed, via the VPH-Share community infrastructure. In this way the benefits of the development will be made available to all, and will encourage uptake of the VPH-Share system. EurValve will take advantage of VPH-Share's own exploitation and dissemination strategy to assist in the process of mutual sustained activity.

The EurValve infrastructure will enable integration with external and bought-in computational and storage resources, greatly enhancing the sustainability of solutions developed. EurValve will ensure deployment of DSS and ancillary services on external hardware, and provide appropriate billing, monitoring and administrative support tools.

2.1.8 Contribution to the Call-Identified Impacts

The PHC-30 call identifies six target impacts for activities in this domain, and EurValve is well-positioned to contribute significantly to all six:

Coherent use of health data with existing knowledge

EurValve rationalises complexity using evidence-based algorithms to provide novel insights into disease processes, and provides likely prognostic estimates for individual patients across multiple treatment alternatives. This exemplifies the aspirations of this objective, uniting patient-specific results with established knowledge to yield improved and valuable healthcare outcomes. EurValve shares the same long-term goal as the entire VPH community: Predictive, Personalised, and Integrative medicine (PPI). *Predictive* means that we should answer clinical questions not with indirect statistical evidence, but with probabilistic predictions made using VPH-based models. *Personalised* means there is the possibility of developing predictive models that are designed to maximise the likelihood of the prediction for a particular patient, based on the availability of as much patient information as possible. *Integrative* means that whenever necessary sub-models describing processes occurring at different temporal or dimensional scales should be composed into a hypermodel that describes all systemic interactions across scales (body, organ, tissue, cell, and molecule). EurValve will achieve and foster the widespread adoption of such an approach.

Design of predictive and therapeutic interventions

The EurValve approach uses prognostic simulation to aid intervention choice. EurValve will construct the first VHD DSS system to combine the systematic data gathering of current, historical and population data with *in silico* simulation to predict patient outcomes. In doing so it is trail-blazing the concept at the core of PHC-30, and demonstrating that, however useful an assessment based on the current data may be, the clinician's understanding is assisted by the examination of alternative prognostic scenarios under alternative therapeutic regimes.

Better management of complex clinical situations

EurValve brings consistent, maximal analysis, to the complex field of cardiac care, and it has been this need to cope with complexity that has driven the entire Virtual Physiological Human endeavour - the logical migration of the successful use of structural and fluids analysis in general engineering analysis to the healthcare domain. We can expect to see increasing use of EurValve technology across many areas of medicine, yet we would emphasise that although the initial applications have naturally sought out the most difficult of problems, the *in silico* approach is effectively a computational framework that can be applied at all levels of healthcare management, and the integration of the simpler decision processes into the same computational paradigm should not - will not - be ignored.

Use of same information by different services

Data re-use has rightly become a mantra for researchers seeking to feed their predictive analytical systems with the fullest range of phenotypical information. Yet perhaps the greater need is for efficient use of clinical data at the point of care, between cooperating clinical teams. Much benefit has followed from the introduction of the multi-disciplinary

team concept, enabling the pooling of resources and skills in the pursuit of comprehensive care. Yet, again, it is in satisfying the needs of a pervasive IT system that we will ultimately complete the translation to a single integrated approach to healthcare. EurValve will bring this discipline to cardiac care, by requiring centralised and consistent use of maximal data across all participants in the care pathway.

Better control and inter-service coordination

Just as with the shared availability of consistent data, so the workflow-driven concept behind *in silico* systems can stand as an example of the way in which automated systems such as that driving EurValve will be capable of orchestrating the many players in the healthcare continuum. The gentle computational revolution that has started with the need to understand the complexity of the disease process will ultimately be seen as the answer to the complexity of the entire healthcare paradigm, and EurValve will be an important exemplar for improving inter-service coordination.

A consistent view of a patient's care needs.

And again, with the sharing of data and the orchestration of service delivery that follow from a centrally-driven care mechanism comes the consistent presentation of patient-related information from a common repository, with no ambiguity. And with all members of the care team able to see only a single consistent version of the patient's status, the associated decision tree and the care pathway, the opportunity for error in the care delivery process is removed. This consistent behaviour at the treatment interface has a spin-off benefit for the philosophy of disease understanding, as having a consistent presentation mechanism driven by consistent data encourages a move towards an integrated view of the disease process that contains no contradictions, leading to the formation of a consistent domain understanding built on the defined Digital Patient.

2.1.9 European Dimension, International Positioning

The pan-European VPH-Initiative operates in a competitive world environment. In an academic context the Commission outlined in its original vision that advanced integrative biomedical research can be achieved only through a common European effort, and we would hope both to foster and to benefit from this environment. However EurValve is intended to develop a practical system with commercial exploitation potential, and for this there is an additional need for awareness and planning around the areas of regulation and technical standards.

For the international academic interface, EurValve partners are highly experienced in European project activity as identified in section 1.3.3. The consortium partners are, or have been, active in several policy initiatives such as ehealth Innovation (www.**ehealth-innovation**.eu) and Avicenna.

2.1.10 Impact at the level of the Work Programme

As already described in some detail above, this proposal assembles a highly interdisciplinary research team focused on a clearly defined medical and public health challenge where ICT-based solutions are expected to render great benefits in the foreseeable future. The ageing of our societies is a great achievement, not the least due to advances in medicine, and this project will contribute to our health systems' better being able to cope with the added strain due to these trends.

Responding to the challenge of Health, Demographic Change and Wellbeing, research and innovation under Horizon 2020 is an investment in better health for all. It aims to keep older people active and independent for longer and supports the development of new, safer and more effective interventions. R&I under Horizon 2020 also contributes to the sustainability of health and care systems. Under this challenge it is expected that projects funded under this topic aim at four impacts, all of which are explicitly addressed by the EurValve project:

Improve our understanding of the causes and mechanisms underlying health, healthy ageing and disease;

Through the maximally-characterised decision support model to be incorporated into EurValve, the multiple factors affecting VHD will be catered for to an extent never before possible. The resulting multifactorial model will provide enviably comprehensive analysis of each individual patient's circumstances, allowing the fullest range of treatment options to be considered, ranked and offered for clinician guidance. The development process will unlock the information already contained in the contributing models, offering an outstanding opportunity for making explicit the underlying disease mechanisms.

Improve our ability to monitor health and to prevent, detect, treat and manage disease

It is perhaps unusual to find a domain that has been so well-served by sophisticated research and modelling developments as cardiac care, yet where the transition to clinical care has been so uneven. Whilst the reason for this has almost certainly been the difficulty in identifying a sufficiently well-characterised subdomain to offer a pathway to clinical exploitation, the consequence for EurValve is that there is an ideally rich library of effective models available. Now with the carefully-chosen VHD clinical domain identified as an ideal target for decision support the opportunity for transforming the diagnosis and treatment landscape has arrived.

Support older persons to remain active and healthy;

VHD is a disease of old age, affecting a significant proportion of the elderly population, and in need of sophisticated support in the identification of optimised therapy personalised to the patient's exact needs. By ensuring that each patient is optimally treated from the outset, EurValve will provide a major enhancement to the clinical repertoire for treatment, and make the first significant *in silico*–based improvement to survivability for the ageing VHD population.

Test and demonstrate new models and tools for health and care delivery

A concept gaining currency in the *in silico* community is that there is merit in considering the possible extension of the automated techniques employed in simulation-based workflows to the design of the very healthcare systems in which they operate. Though any such developments will be slow in arriving, the underlying point is sound: automated workflows containing sophisticated models are mechanisms for the delivery of improved healthcare that might be developed initially to influence patient pathways, and perhaps ultimately entire healthcare systems. EurValve is an important step in the process of bringing multi-competent algorithmic mechanisms to the optimisation of the clinical care process.

2.1.11 Relationship to Standards Development

EurValve will operate in an environment that is rich with guidance on patient care, and EurValve members are active in the furtherance of this practice (see USFD partner description). In the non-cardiac and indeed non-medical arena we expect to interface with experts in these additional areas:

Domain	Correspondents
Cardiology	European Society of Cardiology
Data sharing	ANSI, CEN, DICOM, NEMA, HL7, HFHIR, ISO, xDT
Digital patient representation	WHO, ISO, openEHR, VMR, SMART
Infrastructure design and capabilities	European Cloud, ETSI, Open Grid, Open Cloud, DMTF, Cloud Security All'nce
DSS and medical device categorisation	OLAP, FDA, NIHR, ONC (US), ACDS, CDS Consortium

Table 13: Summary of EurValve Interface with Standards Bodies

2.1.12 Improving innovation capacity, integrating new knowledge (innovation for market need)

Perhaps the single most dramatic development in EurValve is the way in which it is maximally combining existing and new sources of information to build knowledge, not simply at the level of the technology being created, but as a fundamental part of the process that is carried out each time the DSS algorithms are exercised on patient data. There is a new paradigm for built-in knowledge generation that is inherent in the DSS principle, whereby each operation of the mechanism generates outcomes that contribute to the further improvement of the entire system. The emergence of the DSS process is the very mechanism that has been required to enable medical researchers finally to see the fruits of their quest for new knowledge translated directly into benefit for patients and, each time the cycle takes place, to generating further information to drive further research and development. Investment in DSS mechanisms, particularly those linked - as is EurValve - into a process of continual self-improvement, are the exemplification of the much-sought process translating research findings into clinical practice.

2.1.13 Other Environmental and Socially-important Impacts

The table below identifies areas in which an increasingly prevalent culture of automated Decision Support could begin to work beneficially for EU citizens.

Clinical revolution with *in silico* systems	EU citizen benefit
Psychological tenor	Elderly citizens, will see technology as beneficial and non-threatening
Quality of life	Computer systems will be seen as assisting with challenging tasks
Overcoming fear of old age	The promise of increased technical facilities will improve expectations
Patient autonomy and independence	DSS systems are aimed at optimisation, maximising quality of life
Prediction of the evolution of clinical status	Disquiet as to outcomes will be reduced
Reduce risk of societal disadvantage	Empowered patients
Improved systems reduce burden of monitoring	Easier patient care, greater mobility
Increased patient motivation to change physical activity	General improvement in health of the ageing population
Active participation in disease prevention	More informed, healthier citizens
Enlightened self-management	Fulfilment, satisfaction from ownership of processes
Decision sharing	Empathetic consequences of supported decisions
Improved healthcare staff experience, job satisfaction	Quality of life for those associated with patient care

Table 14: Summary of EurValve Environmental and Social Benefits

2.1.14 Barriers/obstacles, framework conditions (such as regulation and standards)

We identify the following issues as being potential barriers to progress in DSS systems generally; in each case we give a possible strategy for overcoming the difficulty.

Challenge	Strategy
Global surveys of Personal Health Systems, barriers and obstacles	Influence opinion within professional bodies
The heterogeneity of the European framework magnifies issues	Strategise based on national characteristics
Legal liability of the service providers and the security of private data,	Develop understand of liability, insurance and methods
Cultural resistance from traditional healthcare systems, institutions	Develop focused presentations, economic, clinical, societal
Social acceptance of CDSS	Patient groups; enhance the positive appraisal, and finally use, in stakeholder groups (patients, medical professionals)
Systemic failures or lock-ins, weak networks, mutual misunderstanding of perspectives and roles, dominant incumbents	Develop understanding of political structures, decision making
Lack of suitable business models, supply-side and demand-side issues; interfaces between supply and demand;	Develop improved strategies based on deep understanding of healthcare policy and strategy
Technical issues (accuracy, stability, architecture, robustness)	Careful staged delivery, evaluation and revision
Lack of standards specifically devoted to DSS, pragmatic interoperability of the available solutions	Participate in development of standards; develop strategy from awareness of market conditions
Technical delay from medical device categorisation of software	Strengthen relationships with standards bodies

Table 15: Summary of EurValve Barriers and Strategies

2.2 Measures to Maximise Impact

2.2.1 Objectives, Strategy and Context

The drive for clinical uptake of VPH tools means that the VPH community is alive to the key importance of dissemination and community building. As published in its original roadmap: "The success of the emerging VPH will be highly dependent upon the information provided to the potential user community. ... The existence of some coordinating body will ensure that resource providers can find an easy way of ensuring that the user base becomes aware of their materials at an early stage, assisting rapid uptake."[117] Within EurValve's activities dissemination will have a central role in order to:

(1) In general, foster the widespread awareness and adoption of the EurValve Decision Support technology

(2) In particular, attract and convince…

- Clinicians to reassess the clinical support paradigm, and appreciate the scientific basis on which the mechanisms are predicated
- Researchers to take up the challenge of applying the EurValve approach to their own clinical domains.

(3) Foster close cooperation with the public and patient groups to build understanding of the benefits.

The wider dissemination activities will embrace informing all relevant stakeholders about the project's results and the implications that these results might have for clinical, industrial and societal users as well as for the research community. This involves disseminating the activities and results of the project to a targeted audience as well as the wider public. The focus lies on active outreach and, given the goal to take the message to patients and the community, activities must extend beyond dissemination of information concerning the technology itself.

The evaluation of the potential for exploitation of outcomes and achievements of EurValve (WP7) will inform and contribute significantly to the dissemination strategy. This will include communicating the benefits that these results will have for faster, more efficient healthcare and aiming for increasing awareness among other target groups. From early into the project we will engage with strategically important bodies including clinical users, health systems operators and health policy decision makers.

2.2.2 Dissemination Modalities and Communications Activities

Key dissemination channels to be employed by this project will include:

- Comprehensive and up-to-date web presence (using modern electronic communications media - website, Facebook, Twitter, other social media - and more
- Conventional types such as email newsletters and printed material,
- Publications in journals and at conferences
- Customised presentations, workshops and via other media to the scientific, medical and political communities.
- Targeted engagements with key clinical, healthcare, regulatory and related-industrial stakeholders

[117] Seeding the EuroPhysiome (2007), p. 82

At the outset the Coordinator's communications assistant will work with the Exploitation task leader and all partners to identify all stakeholders, inside and outside the project. Direct communication with all relevant forums will allow us to reach the various communities.

Name	Time	Dissemination Activities (during the project)
Webs	M01-M36	A project specific web page will be created. The Project Management Office (PMO) at TU/e will make this web-site live by PM06. We will heavily promote by social media and will bi-link, to all partners' web pages.
Slide deck	M06 M18 M30 M36	A slide deck describing the project and current results will be created and regularly updated (on an annual basis at least). This slide deck will be comprehensive and reviewed by all partners. It will contain the slides which are officially accepted to present the project and achievement by any partners. This slide deck will be published on SlideShare and promoted through social media.
Conferences / Events	M06-M36	Organisation and participation in national Meetings and Network events (at least two), where the **EurValve** project results will be disseminated to local communities. • **Partners hosted events:** The partners will present the progress of this project during events / users conference that they are organising to educate their clients on the benefits brought by the new solution. The presentations will be made publicly available. The host will invite other partners to co-present, showing the collaboration value. • **International conferences** The current achievements will be presented to at least 2 selected conferences per year. We will carefully cherry pick the conferences bringing together worldwide experts. Some of these conferences will be the opportunity to organise a round table discussion with the participating (external) experts to present some achievements and collect their feedback. This discussion group will be continued throughout the year through social media. Our presence to these events will be massively promoted through social media. Participation in such events provides the opportunity to the **EurValve** consortium members to invite EC representatives to inform about the progress of the project.
Scientific articles	M24 M36	Scientific papers published in prestigious, peers reviewed journal will be written. Our goal would be to publish at least 1 paper on a yearly basis (with the exception of the 1st year of the project).
Commun-ications	M12 M24 M36	*A Publications Forum will be established as a standing agenda item at the Annual General Assembly. This Forum will encourage and support the publication of project results.* Communication / vulgarisation articles targeting a larger audience (e.g. ANSYS Advantage magazine, 80,000 hardcopies – 25,000 web download) will be prepared on an annual basis. These documents will be shared with the specialised press to encourage them to write and publish about the project and its results. We target 3 press articles per year from year 2.
Press Release	M2 M18 M35	The PMO will publish a regular Project Newsletter, with web distribution plus a small number of hard copies which will be disseminated strategically at key H2020 Health events. We will prepare 3 Press releases: a. When the project starts to announce the scope, partner and frame of the project b. When key results have been obtained (hopefully towards the project half time) c. At the end of the project to detail the achievement
White Papers	M3 M33	We will write 2 White papers: • A **Concept White Paper** to explain the concept we are trying to develop as part of this project. This WP will be very helpful for future client, partners but also the media to understand the scope of this project. This White paper will be ~ 4 pages long and will be written at the beginning of the project. • **Achievement White Paper**: it will describe what we have actually achieved to address this problem and discuss the solution we have developed together with the quantified benefits it is bringing. The promotion of these white papers will be done extensively through social media.
Video	M12 M36	Today, most people are more inclined to spend a couple of minutes to watch a video more than reading a few pages long document. Along the same spirit as the White Papers, we'll create 2 short (<4 min) video . • **Concept Video** explaining the goal of the project; it will include interview of the key partners. • **Achievement Video** showing the end results and interviewing the people who really benefit from the project. The promotion of these videos will be done extensively through social media.

Name	Time	Dissemination Activities (during the project)
Social Media	M1 Till M36	• A specific **public LinkedIn group** will be created to share material and run discussions with anyone interested by the topic. This LinkedIn group will be a way to identify interested clients for the future product exploitation. • A **private LinkedIn group**, by invitation only, will bring together experts in this field to collect experts advices and test / validate new ideas. • A specific **Twitter account** will be created to regularly inform the market on the progresses made in the project; this Twitter account will be used to communicate the presence of the partners to some related events. We will also follow the Twitter of key actors to maintain awareness about the latest progress and events. • **Blogs**: 2 blogs discussing the progress and recent achievements of the project will be published every years. These blogs will be echoed by the blogs of the partners and will be actively promoted through social media (e.g. LinkedIn Group and Twitter)
Collaterals	M12M24 M36	Various collaterals will be developed to explain and promote the project: • **A 4 pages brochure / leaflet**: a first version will be done at the half of the project describing the concept and the first results. An update version will be created towards the end of the projects • **Case Studies**: various case study describing the technical challenges and solutions will be written. The goal would be to create a new case study (on an annual basis (and update existing ones as needed.
Workshop	M30	The PMO will arrange a major demonstration and dissemination workshop in parallel with a targeted clinical conference, selected depending on the maturity of the system.

Table 16: Dissemination Activities

More specific details of each of the communications channels are given below.

2.2.3 Dissemination Media - Journals:

The necessary work will go beyond dissemination of information/results via the Internet, and involve also publications in journals, newsletters of participating partners, etc. and by regularly issuing an electronic newsletter. Also, an initial project flyer and later a more comprehensive brochure will be prepared, and a project logo developed.

Furthermore, opportunities to present project activities and outcomes to a professional, scientific, industrial and policy audience around the world will be taken up, including the following media identified by project partners as their preferred channels for publications:

IT & Biomechanics	Cardiovascular
• The Open Biomedical Engineering Journal which has launched a Special Issue on VPH related research • International Journal of Technology Assessment in Health Care, published by Cambridge University Press • The Open Biomedical Engineering Journal which has launched a Special Issue on VPH related research • International Journal of Technology Assessment in Health Care, published by Cambridge University Press • Computer Methods and Programs in Biomedicine • Philosophical Transactions of the Royal Society • Medical Informatics and Internet in Medicine • IEEE Computer Graphics and Applications • IEEE Engineering in Medicine and Biology • IEEE Transactions of Biomedical Engineering • Journal of Biomechanics • Journal of Biomechanical Engineering • Journal for Numerical Methods in Biomedical Engineering • International journal of computational methods in Bioengineering • Computational Physics • Plos Computational Biology • IEEE transactions Medical Image Analysis • Journal of Web Semantics • International Journal On Semantic Web and Information Systems • ACM Transactions on Computer Systems • Concurrency and Computation-Practice and Experience	• American Heart Journal • American Journal of Physiology • Artificial Organs • Biomedizinische Technik - Biomedical Engineering • Biophysical Journal • Cardiovascular Electrophysiology • Circulation • Circulation Research • Computer Methods in Applied Mechanics and Engineering • ESAIM: Mathematical Modelling and Numerical Analysis • European Radiology • European Heart Journal • Experimental Physiology • Heart • Heart Rhythm • IEEE Engineering in Medicine and Biology • IEEE Transactions on Biomedical Engineering • IEEE Transactions on Medical Imaging • International Journal of Cardiology USFD • International Journal of Medical Robotics and Computer Assisted Surgery • Journal of Biomechanics • Journal of Biomechanical Engineering • Journal of Cardiovascular Magnetic Resonance • Journal of Computation Physics • Journal of Electrocardiology • Journal of Magnetic Resonance Imaging • Journal of the American College of Cardiology • Journal of Thoracic Surgery

IT & Biomechanics	Cardiovascular
• Future Generation Computer Systems • IEEE Internet Computing • IEEE Transactions on Parallel and Distributed Systems • International Journal of High Performance Computing Applications • IEEE Transactions on Information Technology in Biomedicine • Methods of Information in Medicine • BMC Bioinformatics • International Journal of Biomedical Informatics • VLDB journal	• Krankenhaus & Management • Lancet • Magnetic Resonance in Medicine • Medical Image Analysis • Medical Engineering and Physics • Medical & Biological Engineering & Computing • Nature • New England Journal of Medicine • Pacing and Clinical Electrophysiology (PACE) • Radiology • SIAM Journal on Applied Mathematics • Simulation in Healthcare • The Internet Journal of Medical Simulation

Table 17: Dissemination Journals

2.2.4 Dissemination Media - Presentations, Workshops, Tutorials and Seminars:

Personal contacts with stakeholders are an excellent way to promote and demonstrate projects goals and results as well as network with the interested members of the community. To address the potential user communities, present and discuss results, and drive future exploitation, members of EurValve will submit and contribute to the events and annual conferences organised by relevant VPH community projects and institutions, including relevant symposia organised by the Commission. International domain-related events are identified below.

IT & Biomechanics	Cardiovascular
• ISB - International Society of Biomechanics. • IEEE International Symposium on Biomedical Imaging • ICBME - International Conference on Biomedical Engineering, in conjunction with WCB (World Congress on Biomechanics) • ICCB - International Conference on Computational Bioengineering. • Annual International Conference of the IEEE Engineering in Medicine and Biology Society, • Annual CinC Conferences - Computing in Cardiology scientific conferences take place in September each year • BIBE - IEEE International Conference on Bioinformatics and Bioengineering • World Congress on Medical Physics and Biomedical Engineering • European Biomedical Engineering Congress (EMBEC) • International Joint Conference on Biomedical Systems and Technologies, • International Conference on Computational Science (ICCS) • Congress of the European Society of Biomechanics (ESB) • ESB (European Society of Biomechanics), • ASME Summer meeting, • World Conference of Biomechanics • MACII Medical Image Computing and Computer Assisted Intervention • Functional imaging and modelling of the heart. • International Semantic Web Conference (ISWC) • Extended Semantic Web Conference (ESWC) • International Conference on Web Services (ICWS) • World Wide Web Conference (WWW) • ICCS - International Conference on Computational Science • HPDC - High Performance Parallel and Distributed Computing • IPDPS - International Parallel and Distributed Processing Symposium • Euro-Par • Supercomputing • International Conference on Grid and Cooperative Computing (CCGrid) • American Medical Informatics Association (AMIA) Annual Meeting • IEEE International Conference on Bioinformatics and Biomedicine • IEEE Information Technology and Applications in Biomedicine (ITAB) • IEEE Bioinformatics and Bioengineering Conference (BIBE)	• American Heart Association AMC, KCL • American Society for Artificial Internal Organs (ASAIO) • American Society of Mechanical Engineers (ASME), BioengineeringDivision • Annual Meeting of the European Association of Echocardiography • Annual Scientific Sessions of the Heart Rhythm Society • Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology • Bildverarbeitung in der Medizin • Biomedical Engineering Society Meetings (BMES) Charing Cross International Symposium • Computers in Cardiology (CINC) • Computer Assisted Radiology and Surgery (CARS) • Congress of the European Society of Cardiology • Congress of the European Heart Rhythm Association (EUROPACE) • European Association for Cardio-Thoracic Surgeons (EACTS) • European Biomedical Engineering Congress (EMBEC) • European Community on Computational Methods in Applied Sciences (ECCOMAS) • European Medical and Biological Engineering Conference • European Microcirculation Conference • Experimental Biology (USA) • European Society for Artificial Organs • European Society of Biomechanics (ESB) • European Society of Radiology (ESR) • Heart Rhythm • Functional Image and Modelling of the Heart (FIMH) • IEEE International Symposium on Biomedical Imaging (ISBI) • Information Processing in Medical Imaging (IPMI) • International Congress on Computer Assisted Radiology and Surgery (CARS) • International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS) • International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI) • International Conference on Modelling and Simulation (IASTED) • International Council for Industrial and Applied Mathematics (ICIAM) • International Society for Magnetic Resonance (ISMRM) • International Society for Rotary Blood Pumps (ISRBP) • International Symposium. HCSC • International Union of Physiological Sciences (IUPS) • Mathematical Methods in Biomedical Image Analysis (MMBIA) • Radiological Society of North America (RSNA) • Society for Cardiovascular Magnetic Resonance (SCMR) • SPIE Medical Imaging • Symposium "Biomedizinische Technik" of the DGBMT

IT & Biomechanics	Cardiovascular
• ACM SIGMOD International Conference on Management of Data (SIGMOD) • International conference on Very large Databases (VLDB)	• Veith Symposium • World Cardio Agenda, European Society of Cardiology • World Congress of Cardiology • World Congress on Computational Mechanics (WCCM) • World Congress on Medical Physics and Biomedical Engineering

Table 18: Dissemination Conferences

2.2.5 Dissemination - eMedia

EurValve will additionally embrace all eFormat dissemination systems to reach specific communities, matched to the targets of the dissemination topics concerned.

- Website: A website will be the public face of the project, operating as a vehicle for communication of the activities of all partners. Enhanced impact of the EurValve web presence will be achieved through exploitation of links with Insigneo and the VPH Institute. A section of the website will be dedicated to a 'lay summary' of the focus of the project. As the project progresses the website will evolve to exploit links with other content, including the TheraShare.tv platform provided by Therenva. Objectives are to demonstrate the relevance, importance and sophistication of the concept, and to engender desire amongst the public for advanced clinical technologies.
- Newsletter: A EurValve newsletter will be produced by the PMO, providing a total of 3 newsletters over the project duration. This will be published on the project website and disseminated via social media; hardcopies will be considered for project dissemination at events. Objectives are to provide formalised information, provide tangible evidence of progress, and to receive input
- To enhance the public profile of the project, EurValve will establish a YouTube channel to disseminate outcomes. This will include short videos with highlights of the presentations delivered by EurValve researchers. Objectives are to encourage positive public acceptance and desire for such clinical aids.
- Webinars: The project will consider holding a webinar about the project's outputs, providing an up-to-date view of the network via the YouTube channel. The EurValve webinar will be advertised using LinkedIn, VPH Institute and internal communication channels. Objectives are to promote openness and dialogue with specific interest groups.
- News services: Strongly based on the experience gained by all partners, the team will exploit a well-established set of dissemination tools and processes, which includes:
    - Direct contacts with journalists specialised in science & medicine news at the global, European or national level in various member states
    - Access to the AlphaGalileo services, one of the most important science news agencies in the world
    - The VPH news services at Biomed Town and its replacement web systems, an RSS feed subscribed by dozens of other web sites and probably the most important source of news related to the European VPH
    - Access to specialised mailing lists in biomechanics, bioengineering, and clinical research that allow direct email contact to more than 10,000 researchers worldwide
    - Major scientific milestones will also be advertised on specialised mailing lists and forums (BIOMCH-L…)
    - VPH Institute mailing list
    - The SIMBIOS news service on simtk.org, and SIMBIOS training resources
    - EC eHealth, ICT and other newsletters and dissemination media

These generic dissemination resources will be complemented with specific dissemination targets related to all research aspects targeted by EurValve. By the end of the project we expect to have a dissemination portfolio including all key stakeholders worldwide.

2.2.6 Dissemination - Associations and Organisations:

Outcomes of the EurValve project will be communicated and presented to European professional associations and national standards bodies and. In this context, we will also explore how best to complement our dissemination and community building efforts through additional USA-based and global channels.

Furthermore, to widen the scope of community building and assure maximum impact on cooperation, measures will include identifying sub-topic interdisciplinary fields, e.g. with experts from these domains:

- Clinical
- Computing
- Regulatory
- Patient Groups

…in order to tie-in at more congruous levels of interest and thus accelerate interest.

2.2.7 Exploitation Activities

Exploitation in EurValve is performed in a phased sequence of steps in which the business opportunities for the principal, and multiple secondary, outputs are identified, evaluated and taken forward. The sequence is below:

Name	Time	Exploitation Activities (during the project)
Solution	M18 +	When a first workflow is complete and relatively stable, it should be installed locally for being tested and evaluated by project partner "clients", considered as the - clients. The goal of this first release would to collect crucial information for the future exploitation of our solution, including: - Feedback from the end user target - Perceived benefit for the end-users - Integration in their daily activities - Acceptable price for this solution - Suggested improvement for a large scale deployment of the solution
Remote availability	M21	When the solution workflow is getting stable and user friendly, it should be made available on a remote access cluster for future access by clients. - clients will get access to this remote solution to provide feedback as potential future users.
Solution	M24+	The complete workflow will be made available to selected potential clients (not members of the project) to collect feedback and recommendations for the Go To Market Strategy including: - Interest for (large scale) adoption of the solution - Perceived benefit - Acceptable business model and prices - Open mind to share a testimonial
GTM Strategy	M33	The partners meet to discuss the Go To Market (GTM) post project strategy to start addressing key questions such as: - Which structure would is likely to exploit the new product - How the IP will be manage - What would be the OEM agreement - Which business model(s) could be used - Preliminary 5 years business plan - Business expectation for each partner - Post project exploitation planning

Table 19: Exploitation Activities

The exploitation activities are designed to bring careful structure to the process of agreeing and executing exploitation activities for the principal output, supporting partner Therenva in bringing the DSS to the attention of strategy. Post-project exploitation planning will continue the work already carried out in the project to test, evaluate, demonstrate and refine the DSS system both to users of the exiting Therenva systems and to a range of potential users. The well-documented healthcare systems across member states means that the identification of target users is straightforward.

2.2.8 Exploiting other benefits from EurValve

The second exploitation priority is the conduct of the equivalent process from 2.2.7 above for the individual exploitable elements of the other partners work. An early inventory of exploitable items from each partner is tabulated below:

Partner	Exploitable	IP Protection?
USFD	Integrated models	Published; open source
ANSYS	Extensive ROM techniques	Copyright; embedded code
CYFRONET	Extensive secure infrastructure systems	Copyright; embedded code
LTSI	Refined case-based reasoning systems	Copyright
MDC	Improved proteomics assessment systems	Copyright; patent?
Ph_EN	Extended machine learning algorithms	Copyright; ultimately embedded software
Ph_GmbH	Segmentation systems	>10 patents; Copyright; embedded code
STHFT	Refined data collection and management software	Copyright
TU/e	Superior uncertainty tools	Open source
UBRISTOL	Developed methods for clinical assessment	Published; open source

Table 20: Exploitable Benefits

2.2.9 Appropriateness of Measures to Fulfilling Impacts

The presence in the consortium of commercial organisations already active in the domain gives a considerable advantage to the EurValve exploitation strategy, as the methods are already in place, the contacts are identified, and an active customer base exists. The missing elements relate to demonstration of the ease of use of the radically updated system and the value of the resulting recommendations, both targets of the presented strategic exploitation plan. Adaptation to findings in the course of the project is a strength of the multi-staged process that has been designed, and allows for updated strategy in the light of feedback.

Many EurValve partners have direct experience of successful exploitation of software outputs from Framework Programme and other development initiatives. Business planning will be the driver for all exploitation activities, and all exploiting partners will develop their strategies based on timetabled and costed activities driven by exploitation goals. Academic partners will involve their technology transfer offices in the process, and IP will be a fixed item on the agenda of PB meetings. Discussions with the Exploitation & IPR Advisory Board will inform the process continually.

2.2.10 Data Management

EurValve will enshrine the sharing of data in the Consortium agreement, identifying partner rights and timescales. It will be a fundamental premise that no data is accessible to any party, internal or external, without full ethical sanction (see 5.1) and that only de-identified data will be shared within the Consortium. The project will exploit a professional data-handling structure for the secure handling of all project data, and will secure, share, curate and exploit these data as tabulated below:

Data Type	Applicable Standards	Curation	Exploitation/Re-use
Clinical de-identified	EurValve Avatar	Clinical centres	Publishable, VPH-Share
Clinical pseudonymised	EurValve Avatar	Clinical centres	Consortium only
Population	Variable	At source, WP3	Model verification
Analytical/CDSS input	To be developed	WP3, 4, 5	Model verification
Analytical/CDSS output	To be developed	WP3, 4, 5	WP3, 4, 5

Table 21: Data Management

2.2.11 Knowledge Management

EurValve will ensure open access, free of charge, online for any user to all peer-reviewed scientific publications relating to its results. In particular, it will:

- As soon as possible and at the latest on publication, deposit a machine-readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications. Additionally we will aim to deposit at the same time the research data needed to validate the results presented in the deposited scientific publications.
- Ensure open access to the deposited publication — via the repository — at the latest on publication, if an electronic version is available for free via the publisher, or within six months of publication (twelve months for publications in the social sciences and humanities) in any other case.
- Ensure open access — via the repository — to the bibliographic metadata that identify the deposited publication, which must include a persistent identifier."

2.2.12 Consortium Agreement and IPR management

A Consortium Agreement (CA) will be negotiated between all partners, settling among other things the internal organization of the consortium, reflecting what has been described about the project management structure of EurValve.

The CA also covers full rights and responsibilities of participants in respect of the confidentiality of any confidential information disclosed by the partners during the project, as well as the publication and communication of information during the project.

The CA will also provide additional rules to ensure smooth dissemination of the results. Settlements of internal disputes and of course Intellectual Property (IP) arrangements will be part of the CA as well. In principle, resolution of disputes shall be obtained at the court having exclusive jurisdiction according to the law applicable. Other institutions for dispute resolution may be consulted provided the law applicable so permits.

Any result generated before the effective date of the CA (i.e. background) shall remain with the respective party bringing such background to the project. Any result generated by a party after said date, during and within the scope of the project (i.e. Result) whether or not it qualifies for Intellectual Property Right (IPR) protection, shall vest in the party that generated such Results. Any jointly generated Result will be jointly owned where the rights and obligations associated to such jointly generated Result will be regulated in the CA, but in any event each joint owner contributing to the cost of such jointly generated Result shall enjoy an unrestricted right to freely use such jointly generated Result. Throughout the execution of the project, all partners will continuously contribute to the identification of Results that may qualify for IPR protection and will act with the aim of achieving a meaningful outcome for the community following completion of the project.

In case certain results are identified to be essential for the future business opportunities of the involved partners, the necessary steps will be taken to protect such results accordingly. The patenting and other protective measure procedures will proceed along the regulations set forth in the CA.

The IP terms and conditions during the cooperation of EurValve will be based on a royalty free basis. After completion of the project (i.e. during exploitation) access rights to background and to Results could require fair and reasonable compensation, subject to agreement amongst the parties and reflected in the CA.

All access rights needed for the execution of the project and following completion of the project will be granted on a non-exclusive basis, will be worldwide and in principle, will not contain the right to grant sub-license(s), but in any case, shall contain the right to have-made. The CA will further regulate rights and obligations for affiliated entities of a party, where those shall enjoy the same access rights conditions as the party participating in the project, and where such affiliated entities will need to grant the requested access rights to other parties if those are needed for during execution and/or following completion of EurValve.

The CA will also provide in additional rules on the introduction, namely pursuant to notification, of background that has been made available under controlled license terms, e.g. so-called open source licenses. To the extent required for proper use of software results, sub-licensing rights on software results may be regulated in the CA if it is in the best interest of the project dissemination, where such sub-licensing rights shall not be in a manner where the so licensed software results would be subject to controlled license terms. Means to make software results available to the other parties or to the public will be part of the CA if so needed.

3. Implementation

3.1 Workplan

3.1.1 Overall Structure of the Work Plan

The work plan is divided into seven work packages, illustrated in the figure below.

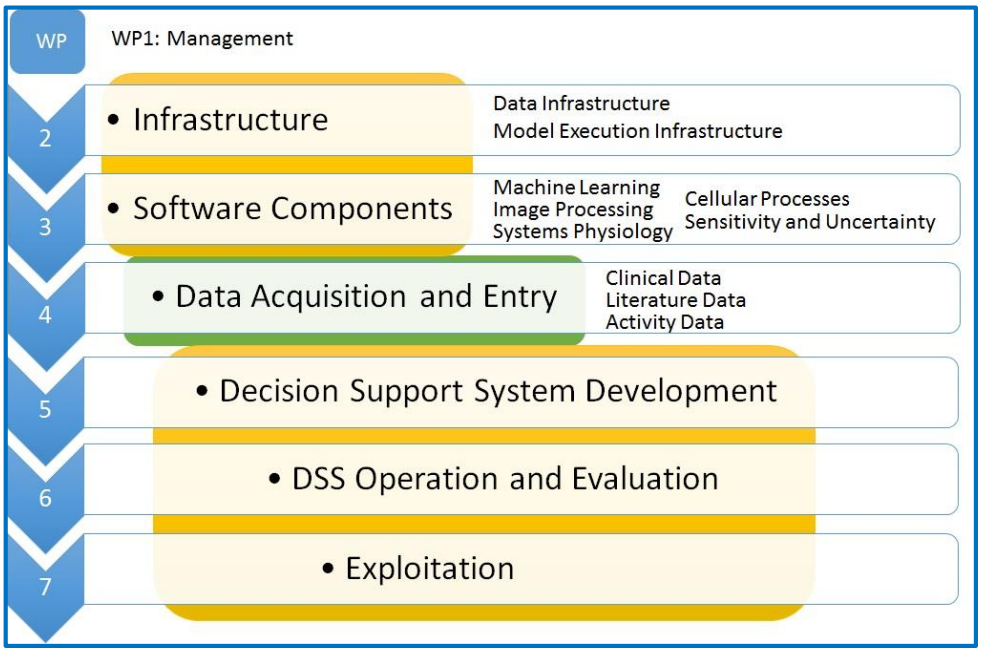

Figure 8: Workpackages in EurValve

3.1.2 Overall Approach and Timing

The primary aim of the Consortium is to develop and to deploy a Decision Support System to assist the clinician to provide the optimal treatment strategy for the individual patient. The concept is to use all of the data that is available about the patient, augmented by population data, by literature data and by types of data that are currently sparsely used in the clinical process, including activity data measured on the individual. Computational models serve to provide improved characterisations of patient physiology and, critically, to predict the effects of potential interventions.

The overall process is complex, and this level of combination of data has not previously been exploited in any clinical scenario. The Consortium recognises the significant challenges in the complexity of the data and of the operations that will be performed on it, and in their integration to underpin the decision support process. The project is organised into five phases, outlined below. There is some overlap between phases because the operation of later elements can begin before the completion of every aspect of the previous phase. The overall strategy is to release stand-alone tools and components at the earliest opportunity, so that the integration can take place on fixed and formal releases. The Decision Support System releases occur later than the toolkit releases for the same reason.

The *Specification Phase* of the project, PM01 – PM06, is dedicated to the careful specification of all the components of the project and their interactions. These include:

- [D4.1 PM03] the context-specific digital patient definition. This data schema represents all of the factors that are associated with the decision process for valve patients, including those that will be exploited for the first time by the DSS that is developed in this project.
- [D2.1 PM03] the data warehouse and data publication suite requirements and functionality check (it is envisaged that the project will use the commercially-available TrialConnect software as the basis of its data management process, augmented as necessary by our own infrastructural components).
- [D3.1 PM04] software components specifications.
- [D2.2 PM04] infrastructure specification.
- [D4.2 PM04] clinical cohort inclusion criteria.
- [D5.1 PM06] decision support system specification, including case-based reasoning module and strategy for integration with EurValve infrastructure.

The *Assembly Phase* of the project, PM03 – PM15, has three parallel activities: These are:

- [D2.4 PM15, D3.2 PM15, D4.5 PM15] **tool and infrastructure development**. It is important to note that all of the operational elements exist already, although substantial refinement and integration will take place in the project. Nevertheless the current availability from the partners of the underpinning tools and technologies make it possible to have in place at the end of the Assembly Phase a beta release suite of stand-alone components, that can be operated on the patient cohort. This is important because a key aspect of the proposal is that we seek to operate machine learning tools on our own data to augment the knowledge base on which the decision support system operates.
- [D2.3 PM08, D4.4 PM15] **data entry**. Early in the assembly phase the clinical centres are trained in the operation of the data infrastructure, and populate the data warehouse with the retrospective and prospective data that is available subject to local ethical approval. The data available at the end of this period is the unprocessed data that is available from the standard or research clinical pathway.
- [D4.3 PM15] **External knowledge assembly**. This includes the representation of the ECS guidelines for valve patients, summarised briefly in section 1.3.5 of this proposal, and the knowledge that is extracted from the literature by the expert partner. This knowledge will be assembled in an appropriate form for presentation to the clinician through the Decision Support System.

The third phase of the project, PM15 – PM28, is the *Augmentation and Integration Phase*. In this phase we will:

- [D6.1 PM28, D4.6 PM28] **augment the data warehouse content** by:
  - Continued collection and entry of data from the study's patient cohort.
  - Operation of the beta release inference tools (part of the machine learning toolkit) to infer missing data where records are incomplete
  - Operation of the beta release tools and models that we have developed to augment the standard clinical data with new characteristic measures that are derived from the operation of the models.
- [D6.2 PM28] **operate the machine learning tools** to develop new knowledge from our own patient cohort.
- [D4.7 PM28] develop the **methods for the interpretation** of the activity data that is a novel component of our proposal, and collect these data prospectively on a subset of the patients that are recruited to the study.
- [D5.2 PM21] integrate the Assembly Phase components into the **Beta Release** of the Decision Support System.
- [D5.3 PM21] develop the Beta Release of the **Case-Based Reasoning** module.

The fourth phase of the project, PM18 – PM30, is the *Candidate Release Phase*. In this phase:

- [D2.5 PM30, D3.4 PM30] the toolkits will be further developed and refined to the final level of maturity for this project, the Candidate Release. It is important for our exploitation strategy that all toolkits are capable of independent operation and exploitation, not only through the Decision Support System that is the primary objective of the proposal.
- [D4.7 PM30] the final integrated report on data collected and augmented by the project will be released.

The final phase of the project is the *Summary and Evaluation Phase*, PM31 – PM36. This sees:

- [D5.4 PM32] the Candidate Release of the Decision Support System, integrating all knowledge generated by the project to PM30.
- [D6.3 PM36] the evaluation of the operation of the DSS on the patient cohort at the clinical centres.
- [D6.4 PM36] the continued support of all software components, including bug fixes, and the formal testing and evaluation of the technical aspects of the system performance, carried out by the leader project's infrastructure leader.

3.1.3 Timing of WPs and Tasks - Gantt chart

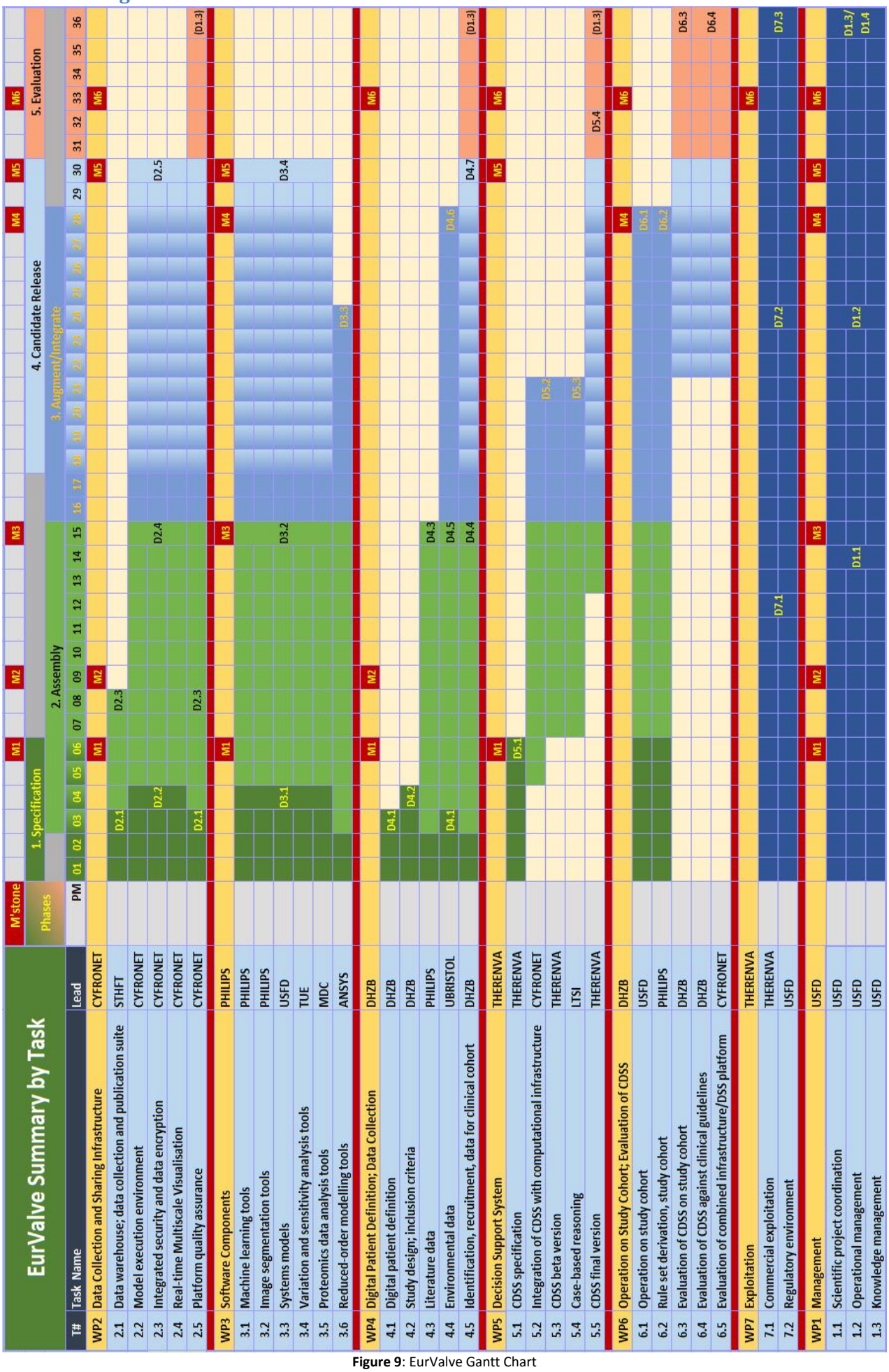

Figure 9: EurValve Gantt Chart

3.1.4 Detailed Work Description (Table 3.1a)

(Table omitted –now in Part A)

3.1.5 List of Work Packages (Table 3.1b)

(Table omitted –now in Part A)

3.1.6 List of Deliverables (Table 3.1c)

(Table omitted –now in Part A)

3.2 Management Structure and Procedures

3.2.1 Introduction

EurValve is a medium-sized project requiring a capable management structure to ensure both strategic and practical implementation according to the project plan. Overall project organisation has been designed to support an objective-driven process in which the eight workpackages are directed both tactically and operationally. The operation and interaction between partners to achieve the execution of the project will be governed by the terms of a formal Consortium Agreement. The Consortium Agreement, which will be based on the DESCA Model Agreement, will include details to formalise confidentiality arrangements, intellectual property rights (IPR), exploitation rights, decision making and change procedures, possible addition of participants and negotiation with third parties, and will define the way in which participants will cooperate after the project ends. The following paragraphs detail the executive and management structures.

3.2.2 General Assembly (GA)

The General Assembly is the formal governing body of the Project, comprised of a voting member from each participating organisation and chaired by the Co-ordinator. Any contract amendment requests will be formally presented to the GA, and subject to vote according to the terms of the Consortium Agreement. Any disputes that cannot be resolved by the Project Board will ultimately be taken to the GA for resolution.

3.2.3 Project Board (PB)

The Project Board is the primary executive body with ample powers to make decisions on daily issues. The Project Board will be composed of the Work package Leaders (WPLs) and chaired by the Scientific Co-ordinator as Executive Director. The PB will supervise and ensure the execution of the Implementation plan described in the section 3.1. It will be responsible for ensuring project progress including the monitoring project milestone fulfilment, and will coordinate the interactions between WPs so that dependencies are managed. The PB will make decisions regarding the implementation plan, exploitation of the project, or resources allocation between WPs. The PB will be in close contact with the Project Management Office (see next section), so that actions can be followed-up in a timely fashion in the Implementation plan, resources can be dynamically allocated and management issues resolved. For this purpose, the PB will meet by teleconference every month, and in a face-to-face meeting every six months; in addition it will be in constant communication using the appropriate electronic tools. The PB will manage the resolution of disputes and matters relating to allocation of funding, as well as situations in which project efficiency might be endangered.

3.2.4 The Coordinator

The Coordinator, USFD, has the overall responsibility for the progress of the Project. The Coordinator steers the scientific work performed in the Project in order to ensure that the results achieved are of the maximum quality in scientific terms and are compliant with the objectives set for the Project. The Coordinator will be supported by the Project Manager, who will be responsible for the daily coordination and scientific steering of the project. The Coordinator delegates to the PMO, but remains responsible for, all aspects relative to project management and operational coordination, including the contacts with the Community when relative to such issues.

Scientific Co-ordinator

The scientific co-ordinator will be Professor Rod Hose. He is an experienced project scientific co-ordinator, having most recently led the 14.4 M€ infrastructure project VPH-Share (2011-2015). He will chair the Project Board as the representative of the Co-ordinator, USFD.

Project Management Office (PMO)

The PMO will comprise a fractional Project Manager and, within USFD Finance, a fractional financial officer. The main duties of the PMO will be to ensure that the project develops appropriately such that all the stakeholders can regard it as a success. The PMO will organise and minute the monthly meeting of the Project Board, and will follow up actions from it. The PMO will be the main contact point with the European Commission.

3.2.5 The Work Package Leaders

Each work package is the responsibility of one contractor, who will act as Work Package Leader. The WPL will have responsibility for day to day coordination of specific work related to their individual work packages. WPL will be assisted by the PMO for management, communication and financial matters, and by the PB for issues related to scientific work. WPL will co-ordinate the implementation of the work package activities as defined in the Implementation Plan, implement solutions for problems, follow-up and co-ordinate participants involved (internal and external to the Project), coordinate the production of the corresponding deliverables and deliver them to the

PMO, identify risks as early as possible and follow them up, and report the progress achieved against that planned. Each participant will be informed how and when to fulfil the commitment to each Work package, through the WPL.

WPL will report to the PMO, which will summarise on-going issues and report in turn to the PB for approval, who will report the GA for critical decisions concerning the Project's development.

3.2.6 Exploitation & IPR Advisory Board (EIB)

The EIB Board, the composition of which will be agreed by the PB, will continuously evaluate the opportunities for the project to generate Intellectual Property and other innovations. This will be done for both tangible and intangible assets and will involve assessing the aims, milestones, and deliverables of the project and determining where the greatest potential to produce information with commercial value will occur. Preliminary screening of existing protocols, applications and new know-how through patent office databases will reveal where the generated data can be protected. The EIB will ensure that the commercial interests of the industrial partners do not enter into conflict, giving support to the WP7 exploitation and outreach activities. As a condition for proper management of knowledge, and with consideration to the participation of academia, research centres, industry and SMEs, with different interests, the IPR strategy will be defined in the Consortium Agreement and all participants will be asked to list pre-existing know-how that they wish to exclude from access by the Consortium. This list will be considered by the partners to be confidential. Specific access policies will also be detailed if necessary in the Consortium Agreement.

The knowledge management framework will enable continuous analysis of output progress within workpackages, permitting the rapid registration of patents where relevant, so that the competitive edge of the project, scientifically and commercially can be enhanced. WPLs will be required systematically to file and report to the PMO new knowledge generated during the period funded by the Commission. The EIB will also report to the PMO on any exploitation opportunities and, importantly, on any conflict between partners.

Any further agreements concluded by the contractors to transfer ownership of knowledge to third parties will ensure that European competitiveness is not endangered and will follow EC rules, giving the Commission 60 days' prior notice.

3.2.7 List of Milestones (Table 3.2a)

(Table omitted –now in Part A)

3.2.8 Critical Risks for Implementation (Table 3.2b)

(Table omitted –now in Part A)

3.3 Consortium as a Whole

The EurValve consortium of thirteen partners has an appropriate balance to achieve the objectives of the project. The primary goal is to create a sophisticated *in silico*-driven decision support system to optimise the care of patients with Valvular Heart Disease, and to evaluate it clinically. The concept builds on an existing software solution from partner THERENVA, and benefits from the experienced imaging systems that are the *forte* of PHILIPS. The central innovation of advanced modelling will be assembled from existing systems already available, and the substantial cluster of processing tools will be developed and refined by the project's academic technology partners (USFD, CYF, LTSI, MDC, TU/e). Refinement and performance optimisation of the main computational system will be conducted by authors ANSYS. Evaluation is the role of three leading EU clinical partners (CATH, DHZB and STHFT). The entire software mechanism is to be housed in a state-of-the-art computational infrastructure developed by seasoned experts CYFRONET. The specialised inclusion of activity monitoring assessment will be contributed by UBRIS, one of two institutions from the UK's prestigious Russell Group (www.**russellgroup**.ac.uk), the other being coordinator USFD itself, which has a strong track record in the co-ordination of major international projects.

3.4 Resources to be Committed

Project Budget

All budgets listed in the A3 forms reflect the estimated costs expected to be incurred in carrying out the project and were calculated according to the accounting principles of the partners, which are subject to formal annual financial audits. The budget for the proposed research work is estimated at €5M.

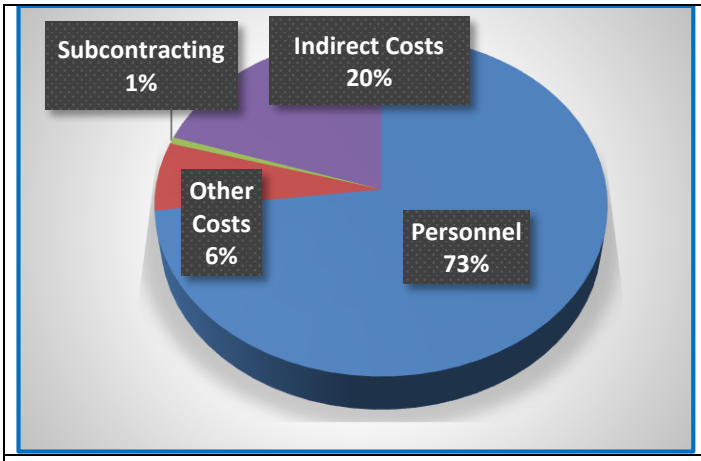

Figure 17: Funding by cost category

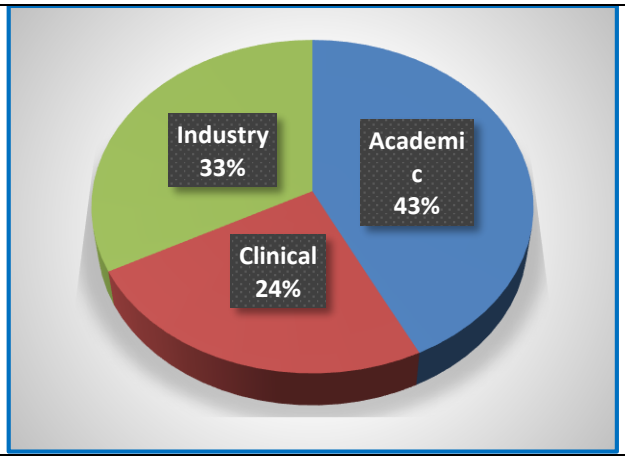

Figure 18: Funding by partner type

For partners with an individual amount of requested funding that exceeds the EC declared limit, compulsory cost certificate costs are accounted for. The budget needed for these cost certificates is included in the management budget.

Manpower Allocation

EurValve will run for 36 months and will mobilise 552 man-months of research effort.

- 44% of the project effort is allocated to academic partners, 23% to clinical partners and 33% to industrial partners
- 71% of the project effort is allocated to technical work packages and 15% of the effort goes to work in the application work package.
- Dissemination and exploitation are expected to make up for 7% of the overall manpower effort
- Finally 7% of the effort will be spent on project management tasks to coordinate the work of the 13 partners involved and report to the EC.

3.4.1 Summary of Staff Effort (Table 3.4a)

(Table omitted –now in Part A)

3.4.2 'Other Direct Cost' Items (Travel etc.) (Table 3.4b)

ParticipantNumber Short Name	4 Cyfronet	Cost (€)	Justification
Travel		38,905	Meetings
Equipment		0	Consumables for analysis
Other goods and services		3600	Audit
Total		42,505	

Partner Cyfronet has relatively low effort in the project, but their workpackage leadership and the nature of their technical contribution requires multiple representation at some meetings and conferences, and their location in Poland attracts slightly lower personnel costs and slightly higher travel costs than average, putting their Direct/Personnel ratio just above the 15% threshold for reporting.

ParticipantNumber Short Name	7 MDC	Cost (€)	Justification
Travel		12,000	Meetings
Equipment		52,000	Consumables for analysis
Other goods and services		0	n/a
Total		64,000	

Partner MDC has low effort in the project, but their analytical work involves the use of consumable materials.

3.4.3 Large Research Infrastructure

No costs to declare

4. Members of the Consortium

4.1 Participants (applicants)

	**University of Sheffield**	**1: USFD**
General Description	The **University of Sheffield** is a member of the UK's prestigious Russell Group of research-intensive institutions. It has a formidable record in computational life sciences research and has collaborated in pan-European EC-funded projects since the earliest Framework Programmes. Having recently established the 130-member Insigneo Institute for *in silico* Research – a joint venture between the faculties of Medicine and Engineering together with Sheffield's very large NHS Hospital Trust – it is able to provide unified access to all aspects of simulation-based medical research. As an important leader in the *in silico* research community, Sheffield has overseen the increasing maturity of mathematical modelling activities within medicine, developing sophisticated framework-based approaches to many aspects, including collaborative development environments, formalised multiscale technologies, secure data-sharing mechanisms, structured algorithmic development processes and generalised sharable workflow technologies. The two senior investigators in this proposal have over fifty years of combined experience in the computational and histopathological investigation of heart valve disease.	
Main tasks, match to profile	USFD will lead the project and will provide and deploy the computational models to assess patient-specific physiology that are at the core of this project. USFD will provide expertise and guidance in regulatory affairs associated with implantable devices.	
Role and Commitment of key people	**Prof Rod Hose**, Professor of Computational Biomechanics at USFD, will be the Principal Investigator (PI) for the project. He is the PI for VPH-Share, and was workpackage leader for valvular disease in euHeart (see below). He was a co-author of the White Paper that launched the Virtual Physiological Human initiative. He joined acadaemia twenty years ago following an early career as an engineering consultant, and has 169 publications indexed in Web of Science with an h-index of 20. **Prof Pat Lawford**, Professor of Physiological Modelling at USFD, will provide input on the regulatory aspects, and on the biological processes. She has 25 years' experience in cardiovascular device development and was responsible for the UK Centre for heart valve evaluation. A member of the British and ISO standards committees for cardiovascular devices and leader of the UK Panel for Heart Valves she was PI for an EPSRC study of the haemodynamics of DVT and PI in Sheffield for FP7 COAST. **Prof Richard Clayton**, Professor of Computational Physiology at USFD, will provide input to and supervision of the development of the models to associate proteomic data with heart contraction. His has particular interest in cardiac arrhythmias and the modelling of uncertainty, and he leads the EPSRC-funded POEMS (Predictive Modelling for Healthcare Technology through Maths) network. **Dr Keith McCormack** will be principal administrator for EurValve. He has over 15 years' experience in the control of EC and national *in silico* projects, most recently in VPH-Share.	
Relevant Publications and/or Research / Innovation Products (Max 5)	Weese, J., Groth, A., Nickisch, H., Barschdorf, H., Weber, F. M., Velut, J., Hose, D. R. (2013). *Generating anatomical models of the heart and the aorta from medical images for personalised physiological simulations*. Med Biol Eng Comp. Brown, A. G., Shi, Y., Marzo, A., Staicu, C., Valverde, I., Beerbaum, P., Lawford P.V., Hose, D. R. (2012). *Accuracy vs. computational time: translating aortic simulations to the clinic*. J Biomech, 45(3), 516-523. Smith, N., de Vecchi, A., McCormick, M., Nordsletten, D., Camara, O., Frangi, A. F., Hose D.R., Rezavi, R. (2011). *euHeart: personalised and integrated cardiac care using patient-specific cardiovascular modelling*. INTERFACE FOCUS, 1(3), 349-364. Shi, Y., Lawford, P., & Hose, R. (2011). *Review of zero-D and 1-D models of blood flow in the cardiovascular system*. Biomed Eng Online, 10, 33. Hose, D. R., Narracott, A. J., Penrose, J. M., Baguley, D., Jones, I. P., Lawford, P. V. (2006). *Fundamental mechanics of aortic heart valve closure*. J Biomech, 39(5), 958-967.	
Relevant Previous Projects (Max 5)	**VPH-Share**: Leader of 14.4M€ Integrated Project developed computational infrastructure for data handling and model execution. Developed and deployed model sensitivity analysis tools. **euHeart**: Largest single Integrated Project (16.9M€) in domain of Virtual Physiological Human, developed models and tools for analysis of cardiac and cardiovascular systems. WP leader for heart valve disease application. **Discipulus**: Roadmap for the Digital Patient	
Infrastructure Equipment	Insigneo Institute for In Silico medicine, formal collaboration between University and Sheffield Teaching Hospitals Foundation Trust. Computational and data infrastructures.	

ANSYS	Ansys France SAS	2: ANSYS
General Description	ANSYS France SAS is a subsidiary of American company ANSYS Inc, the worldwide leader in engineering simulation market. ANSYS is the leading engineering simulation software developer based in 40 countries across the world employing more than 2,500 employees. Created in 1970, we are exclusively focusing on the development of engineering simulation software covering all necessary physics such as fluid, structure, electromagnetic and acoustic. We complete our portfolio by providing full system and software modelling capabilities. The company primarily grew in the Nuclear, aeronautic and automotive industries more mature with the large scale adoption of engineering simulation across the product development process. During the last two decades, the medical device and pharmaceutical industries have progressively embraced simulation as part of the in silico evolution. Today, ANSYS software is used by 80% of the 50 largest biomedical companies including the top 15. ANSYS France SAS, with more than 140 employees, mainly provides technical support in simulation and also include a development team of 30 engineers. This development team leads ANSYS research in multi body dynamics, response surface, optimisation, probabilistic and reduced order modelling techniques. Moreover the ANSYS France Research team is a centre of excellence for patient specific simulation.	
Main tasks, match to profile	In accord with its expertise, ANSYS will lead Task 3.4 focused on population based modelling and reduced order modelling. ANSYS will also contribute to the exploitation plan in WP7.	
Role and Commitment of key people	**Michel Rochette** graduated from the University of Nice, in 1990 where he obtained a PhD degree in mathematics. He founded CADOE (math company for 3D parametric simulation in 1994). After the acquisition by ANSYS he has been leading the research for two main topics: Patient specific simulation and Reduced Order Modelling. His research team has 2 senior research engineers and 5 PhD students mainly focused on patient specific simulation. As the leader of the ANSYS medical initiative he manages partnership with academic Labs, University Hospitals, Medical software vendors, medical devices companies and medical imaging companies. He is in charge of the development and validation of medical vertical applications developed with partners. **Christelle Boichon Grivot** graduated from the Ecole Nationale Supérieure de l'Aéronautique et de l'Espace, Toulouse, France, in 1993 where she obtained an engineering degree specialising in Aerospace and a Master's degree in Fluid Mechanics. She obtained a PhD degree in Fluid Mechanics from the Institut National Polytechnique de Grenoble, Grenoble, France in 1997 after a 3 year PhD student contract in the French atomic agency (CEA Grenoble). She has been working at ANSYS France in Lyon since 2002. Her main area of interest concerns the numerical methods (optimisation, acceleration methods and reduced order models) and the application of numerical simulation in medical field. **Valéy Morgenthaler** graduated from the Ecole Nationale de Mécanique et d'Aérotechnique (ENSMA) where he obtained an engineering degree and a Master's degree specialising in Combustion in 1995. He obtained a PhD in Combustion from Doctoral School in Engineering and Aeronautics from ISAE/ENSMA. He joined the National Aerospace Laboratory from Japan in 1999 as a Research fellow where he continued his studies on aerospace propulsion. He was hired by ANSYS in 2001 as Technical Account Manager for Aerospace Industry. He finally join ANSYS research group in 2014 where he is developing both reduced model techniques and Biomedical applications in CFD.	
Relevant Publications and/or Research / Innovation Products (Max 5)	Dubini, G., Guarneri, M. R., Clapworthy, G., Katsaounis, N., Lawford, P., Petrakis, E., **Rochette M,** Silvestro C, Testi, D. (2013, November). Pre-surgery planning in vascular procedures: an introduction to the **RT3S** Project. In Bioinformatics and Bioengineering (BIBE), 2013 IEEE 13th International Conference on (pp. 1-4). IEEE. Giacoma, A., Dureisseix, D., Gravouil, A., & **Rochette, M**. (2014). A multiscale large time increment/FAS algorithm with time-space model reduction for frictional contact problems. International Journal for Numerical Methods in Engineering, 97(3), 207-230. Giacoma, A., Dureisseix, D., Gravouil, A., & **Rochette, M.** (2014). Toward an optimal a priori reduced basis strategy for frictional contact problems with LATIN solver. Computer Methods in Applied Mechanics and Engineering. Kaladji A., Dumenil A., **Rochette, M**., Horner M., Castro M., Göksu C., Esneault S., Lucas A., and Haigron P. (2011). Quantification of deformations during endovascular abdominal aortic aneurysm repair using finite element simulation. DA / NHLBI / NSF Workshop on Computer Methods for Medical Devices: Validation of Computer with Nonclinical Models. Silver Spring, MD, USA. September 2011.	
Relevant Previous Projects (Max 5)	VPHOP (EU FP7) 2008 – 2012 Risk of rupture for osteoporotic bones. Development by ANSYS of statistical shape modelling techniques. RT3S (EU FP7) 2011 – 2014 Real time simulation based on Reduced Order Modelling developed by ANSYS. Application to risk of fatigue rupture for peripheral stents. ENDSOSIM: Grant from the French National Research Agency on "Predictive and patient-specific numerical simulations of endovascular interventions"	
Infrastructure and Equipment	Numerical simulation expertise and professional training.	

	Catharina Hospital	3: CATH
General Description	The **Heart Center of the Catharina Hospital** (Eindhoven, The Netherlands) treats the largest patient volume of all centers in the Netherlands. More than 100 percutaneous aortic valve implantations (TAVI) are performed annually and the Heart Centre also has a percutaneous mitral valve treatment programme. Over 2500 percutaneous coronary interventions are performed annually (both elective and urgent). The Heart center of the Catharina Hospital performs clinical and basic scientific research and has a vivid scientific partnership with the Technical University of Eindhoven. The key person representing the Heart Center of the Catharina Hospital in this proposal has over 10 years of experience in the field of clinical and basic research and is currently steering committee member for some international randomised clinical interventional trials.	
Main tasks, match to profile	The main task of the Catharina Heart Centre will be data collection for the DSS.	
Role and Commitment of key people	**Dr. Pim A.L. Tonino** (male), is interventional cardiologist in the Catharina Hospital and obtained his PhD degree (topic of thesis: FFR) at the Eindhoven University of Technology. He is specialised in percutaneous heart valve interventions (TAVI, mitraclip and mitral valve) and FFR. His PhD thesis (Technical University of Eindhoven) was based on clinical studies with FFR (FAME study). He published >30 articles in international journals. His current research activities comprise membership of the FAME 2 steering committee and several studies on the subject of TAVI.	
Relevant Publications and/or Research / Innovation Products (Max 5)	Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med. 2014 Sep 25;371(13):1208-17.* Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. *Circulation. 2013 Sep 17;128(12):1335-40.* Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med. 2012 Sep 13;367(11):991-1001.* Angiographic versus Functional Severity of Coronary Artery Stenoses in the FAME Study: Fractional Flow Reserve versus Angiography in Multivessel Evaluation. *J Am Coll Cardiol 2010;55;2816-2821* Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *N Eng J Med. 2009; 360: 213-24*	
Relevant Previous Projects (Max 5)	**FAME 2:** steering committee member **FAME 1:** steering committee member **Meetbaar Beter:** one of the developers of Dutch national database on outcome and quality in TAVI	
Key Items of Infrastructure and Equipment	High volume TAVI centre. Dedicated research personnel for support with data acquisition. Delivering high quality data for DSS.	

	Academic Computer Centre CYFRONET AGH	4: CYFRONET
General Description	The **Academic Computing Centre CYFRONET AGH** is an autonomous unit, both organisationally and financially, of the AGH University of Science and Technology in Krakow. CYFRONET is one of the largest Polish supercomputing and networking centres and the leader of the Polish PL-Grid Infrastructure for e-Science. In cooperation with the top Polish and European universities, CYFRONET designs, develops and deploys large-scale computing infrastructure solutions dedicated to scientific research. Thousands of computational analyses are run every day on HPC equipment managed by CYFRONET and connected with a high-throughput network backbone to key laboratories in Poland and Europe. CYFRONET research teams have extensive experience in European collaboration, dating back to FP5 research projects – including direct involvement in development and deployment of custom research tools in the life science and medicine domains.	
Main tasks, match to profile	According to its expertise, CYF will lead the Infrastructure Work Package 2, where it will be responsible for delivering efficient, scalable, secure and robust valve DSS model execution environment. CYF will also participate in integration-related tasks of Work Package 5.	
Role and Commitment of key people	**Marian Bubak** is a senior staff member at ACC CYFRONET AGH, an assistant professor at the Department of Computer Science AGH, and the Professor of Distributed System Engineering at the University of Amsterdam. He has authored about 230 papers in this area, and he served key roles in series of EU-funded projects, including CrossGrid (the Architecture Team leader), K-WfGrid (the Scientific Coordinator), CoreGRID (member of the Monitoring Committee), and ViroLab, GREDIA, UrbanFlood, MAPPER and VPH-Share (WP leader). Prof Bubak will lead WP2. **Maciej Malawski**, an assistant professor at the Department of Computer Science AGH and a senior researcher at ACC CYFRONET AGH, is a co-author of over 50 international publications in the area of distributed computing, resource management and support for scientific applications. He is involved in the EU ICT VPH-Share project, where he develops Atmosphere cloud platform for biomedical applications. He will be responsible for leading the research and development of Model Execution Environment.	
Relevant Publications and/or Research / Innovation Products **(Max 5)**	**1. Bubak, M**., Kitowski, J. and Wiatr, K. Eds., *eScience on Distributed Computing Infrastructure*, LNCS vol. 8500. Springer, 2014. 2. **Bubak, M.** et al.: *Virtual Laboratory for Collaborative Applications*. In: M. Cannataro (ed.) Handbook of Research on Computational Grid Technologies for Life Sciences, Biomedicine and Healthcare, Chapter 27, pp. 531-551, Information Science Reference, IGI Global (2009) 3. Sloot, P., Altintas, I., **Bubak, M.**, Boucher, Ch.,: *From Molecule to Man: Decision Support in Individualized E-Health*, IEEE Computer Society, vol. 39, no.11, pp. 40-46 (Nov. 2006) 4. **Malawski, M.**, Figiela, K., Nabrzyski, J.: *Cost Minimization for Computational Applications on Hybrid Cloud Infrastructures*. Future Generation Comp. Syst. 29(7): 1786-1794, 2013 5. Rycerz, K., Ciepiela, E., Dyk, G., Groen, D., Gubala, T., Harezlak, D., Pawlik, M., Suter, J.J., Zasada, S., Coveney, P.V., **Bubak, M.**: *Support for Multiscale Simulations with Molecular Dynamics*. ICCS 2013: 1116-1125	
Relevant Previous Projects **(Max 5)**	**VPH-Share**: Developed computational environment Atmosphere for complex simulation execution and visualisation. Deployed private computational cloud infrastructure. **Mapper**: Developed computational tools for multiscale simulations. This included work on in-stent restenosis simulations in support of cardiovascular research. **PL-Grid:** Develops and deploys solutions dedicated to life sciences and personalised medicine. Apart from provisioning considerable computing power and storage capacity, CYF has also implemented a series of high-level online services for life scientists and healthcare. **UrbanFlood:** Developed an internet-based hosting platform for Early Warning Systems and validating it for flood decision support in urban areas.	
Key Items of Infrastructure and Equipment	CYF operates an extensive high performance computing, networking and data storage infrastructure, including the Zeus cluster (370 TFLOPS) and the Prometheus cluster (1.65 PFLOPS, under installation). CYF disk storage resources currently total 2.5 PB, with a tender underway to procure 3.7 PB in additional space. This infrastructure would be made available to members of the EurValve consortium. We are also specialising in provisioning on-demand cloud-based solutions for specific research projects. On top of our IaaS stack we provide a series of dedicated online services for bioinformatics, data management (https://data.plgrid.pl/) and complex analytics workflows [27] (among others) to ease access to these resources for our users.	

DEUTSCHES HERZZENTRUM BERLIN STIFTUNG DES BÜRGERLICHEN RECHTS	German Heart Institute Berlin	5: DHZB
General Description	**Deutsches Herzzentrum Berlin** (German Heart Institute Berlin, DHZB) is one of Europe's largest Heart Institutes. The research activities of the DHZB cover almost all emerging fields of cardiac diagnostic and therapy, which is reflected by more than 120 peer reviewed publications annually. One major research focus is on non-invasive cardiovascular imaging of patients in all age groups (from infancy to late adulthood). Research of imaging based modelling has been successfully introduced in the past years and is currently applied in several clinical conditions (including heart failure in mitral and aortic valve disease, pulmonary stenosis, aortic coarctation). In addition modelling of blood flow in new valve substitutes is part of the DHZB research (EU FP7 "life valve" project). DHZB has been the leading clinical partner in a recent modelling validation trial (EU FP7 "Cardioproof") where mechanical valve simulations and virtual treatment have already been key aspects. The imaging science group of the DHZB covers the full spectrum of cardiovascular research that ranges from the development of hard- and software, the conduction of small and large animal research, translational science and the lead in clinical multicentre studies. The DHZB has close international ties and long standing collaborative projects with some of Europe´s leading research institutes. In addition, the DHZB is an important partner of the German Centre for Cardiovascular Research (DZHK; http://dzhk.de/) that is currently Germany's largest joint research initiative in cardiovascular medicine. It is part of the core lab for image processing that was initiated by the German Competence Network more than 8 years ago. In this work, the DHZB contributed to build-up the world largest data base of highly standardised CMR imaging datasets from which reference values can be used in EurValve.	
Main tasks, match to profile	In EurValve, DHZB has the role of the leading clinical partner. Based on previous experiences DHZB will provide expertise and will be responsible for the build-up of a clinical research database in WP 2 that will include a digital image repository. In WP 4 DHZB will define digital patient data, assembly data for the clinical cohort and coordinate the clinical phase of the project with the other hospitals involved. Additionally the identification of the clinically relevant literature will be a substantial deliverable. In WP 6 DHZB will be responsible for a randomised controlled experiment that evaluates the efficiency against current clinical guidelines and involves clinical professionals from the field of Cardiology.	
Role and Commitment of key people	**Prof Volkmar Falk** is the head of the Heart and Thoracic Surgery department at DHZB. As a surgeon he has many years of clinical experience and a strong scientific interest in new methods of heart valve surgery. **Prof Titus Kühne** will be the clinical leader of the project. He is formally affiliated with the DHZB and the Charité, Medical University Berlin where he has a Professorship for Non-invasive Cardiovascular Imaging. At the German Centre for Cardiovascular Research / German Competence Network - CHD he is heading the imaging infrastructure section. He has expertise in imaging of all age groups (from infants to the elderly) and strong international scientific merits concerning the MR imaging modalities (including 4D blood flow) and post-processing framework, that will be used in EurValve. He also is the PI in the Cardioproof project that focused on model validation. **Dr. Leonid Goubergrits** is an engineer from the field bio-fluid-mechanics. He has a strong interest in Computational Fluid Dynamics and has been an activity leader in the validation process of Cardioproof. **Dr. Marcus Kelm, MD** is a physician-scientist with many years of experience in research and cardiovascular medicine. He has a strong interest in cardiovascular imaging and translational research, and he has enrolled patients in clinical studies including Cardioproof. He introduced a novel method of cardiovascular profiling that is also of relevance in this project.	
Relevant Publications and/or Research / Innovation Products (Max 5)	Pressure fields by flow-sensitive four-dimensional velocity-encoded magnetic resonance imaging in patients with aortic coarctation. Riesenkampff E, Fernandes J, Meier S, Goubergrits L, Kropf S, Schubert S, Berger F, Henneumuth A, Titus Kuehne T. JACC – imaging. Accepted 2014 Emmert MY, Weber B, Falk V, Hoerstrup SP. Transcatheter tissue engineered heart valves. [Review] Expert Rev Med Devices 2013 Small Animal Look-Locker Inversion Recovery (SALLI) for Simultaneous Generation of Cardiac T1 Maps and Cine and Inversion Recovery-prepared Images at High Heart Rates: Initial Experience. Messroghli DR, Nordmeyer S, Buehrer M, Kozerke S, Dietrich T, Kaschina E, Becher PM, Hucko T, Berger F, Klein C, Kühne T. Radiology. 2011 Oct;261(1):258-65. Three-dimensional alignment of the aggregated myocytes in the normal and hypertrophic murine heart. Schmitt B, Fedarava K, Falkenberg J, Rothaus K, Bodhey NK, Reischauer C, Kozerke S, Schnackenburg B, Westermann D, Lunkenheimer PP, Anderson RH, Berger F, Kühne T. J Appl Physiol. 2009; 107(3):921-7 (Awarded at the DGPK meeting 2010)	

	Integrated assessment of diastolic and systolic ventricular function using diagnostic cardiac magnetic resonance catheterisation. Validation in pigs and application in a clinical pilot study. Schmitt B, Steendijk P, Lunze K , Ovroutski S, Falkenberg J, Rahmanzadeh P, Maarouf N, Ewert P, Berger F, Kühne K. J Am Coll Cardiol: Cardiovascular Imaging 2009; 2:1271-1281 (with editorial
Relevant Previous Projects (Max 5)	**Cardioproof** Cardioproof is a proof-of-concept project that (1) Consolidates the outcomes of previous VPH projects, (2) checks the applicability and effectiveness of available predictive modelling and simulation tools and (3) validates them in interrelated clinical trials conducted in three European centres of excellence in cardiac treatment. Virtual Models and interventional tools developed in Cardioproof will be clinically validated, and ready to use methods will be available for EurValve, also in conjunction with established workflows at DHZB as a clinical partner to ensure data quality, and that enables the seamless integration into the DSS for a collective of patients with heart valve diseases. **MD Paedigree** DHZB had been a clinical partner in this clinically-driven and strongly VPH-rooted project, that pursues an improved interoperability of paediatric biomedical information, data and knowledge by developing together a set of reusable and adaptable multi-scale models for more predictive, individualised, effective and safer paediatric healthcare. **SMART** SMART aims to establish individualised strategies for the prevention and management of heart failure by early detection of the physiological, genomic, proteomic and hemodynamic mechanisms that lead from one common cause of ventricular dysfunction (pressure overload) to maladaptive remodelling and irreversible HF. To cope with the complexity of heart failure, SMART will interrelate models describing the interplay between genome, proteome and cell function, regulating hormones, tissue composition and hemodynamic whole organ function up to a whole body description of a patient and patient cohorts.
Key Items of Infrastructure and Equipment	DHZB is one of the largest European centres treating heart valve disease in a large variety of age groups. With the experience from previous VPH trials a high quality standard of imaging data of different modalities will be available. Clinical data exchange using the TrialConnect software platform will allow technical partners seamless data access, processing, and validation workflows that will be substantial in the DSS development

	University of Rennes 1 - LTSI	6: UR1
General Description	The Signal and Image Processing Laboratory (LTSI – INSERM U1099) is a joint Research Unit of the INSERM and the University of Rennes 1. The research is thus conducted in strong cooperation with physicians, some of them being affiliated both to LTSI and to clinical organisations. Research activities of LTSI lie at the interface of Information Technology and Health sciences. Their objectives are methodological, technological and clinical with two main aims: data interpretation and decision-making. They are based on the kernel `signal-model-image', these three components bringing an essential added-value. The LTSI has over 140 members including 70 permanents (EC, C, & IATOS ITA) and university hospital staff. The laboratory is structured into five teams (SESAME, SEPIA, MetriQ, IMPACT, MEDICIS), each of which was rated A+ in the last assessment of AERES (2011). The team organisation of LTSI is backed by transversal projects of methodological research exploiting synergies between signal and image processing, sensors and modelling. Each team is focused on a limited target and was built around a multidisciplinary group able to integrate the latest physiological knowledge in the field, and to identify the underlying methodological issues. Among these, the activities of IMPACT team, which will be more specifically involved in the project, focus on decision support through images and modelling to plan and guide surgical and therapeutic procedures. The works aim particularly at addressing main issues in terms of public health. The challenge is to build the future personalised therapeutic strategies in the fields of cardiovascular and cancer diseases where organs and lesions are soft and deformable within the course of treatment and observed through multimodal and multi-scale N-dimensional data.	
Main tasks, match to profile	LTSI will focus on cases representation and similarity to provide the decision support system with case based reasoning facilities.	
Role and Commitment of key people	Pascal Haigron is Professor at the University of Rennes 1, Rennes, France. He is responsible of the research team IMPACT (Images and Models for Planning and AssistanCe to Therapy and surgery) at LTSI. He will coordinate the works on case based reasoning to be integrated in the decision support system. Mireille Garreau is Professor at the University of Rennes 1, Rennes, France. Her research experience is related image processing and knowledge-based systems with applications in biomedical engineering and cardio-vascular imaging. She will contribute to cases representation and similarity for case based reasoning.	
Relevant Publications and/or Research / Innovation Products (Max 5)	Garreau M, Coatrieux JL., Collorec R, Chardenon C. A knowledge-based approach for 3-D reconstruction and labeling of vascular networks from biplane angiographic projections. IEEE Transactions on Medical Imaging, 1991, 10(2), 122-131. Kaladji A, Lucas A, Kervio G, Haigron P, Cardon A. Sizing for Endovascular Aneurysm Repair: Clinical Evaluation of a New Automated Three-Dimensional Software. Ann Vasc Surg. 2010 Oct;24(7):912-20. Ruggieri VG, Anselmi A, Wang Q, Esneault S, Haigron P, Verhoye J-P. Computed Tomography Image Processing to Detect the Real Mechanism of Bioprosthesis Failure: Implication for Valve-In-Valve Implantation. Journal of Heart Valve Disease. 2013 Mar;22(2):236-8. Tavard F., Simon A., Leclercq C., Donal E., Hernandez A.I. and Garreau M., Multimodal Registration and Data Fusion for Cardiac Resynchronisation Therapy Optimisation. IEEE Transactions on Medical Imaging, 2014, 33 (6), 1363-1372. El-Fakdi A, Gamero F, Melendez J, Auffret V, Haigron P. eXiTCDSS: A framework for a workflow-based CBR for interventional Clinical Decision Support Systems and its application to TAVI. Expert Systems with Applications. 2014 Feb 1;41(2):284-94.	
Relevant Previous Projects (Max 5)	**ITEA2 Mediate**: Leader of the TAVI demonstrator. Contribution to the development of The computer aided endovascular navigation system for Transcatheter Aortic Valve Implantation (TAVI). Constitution of the database and contribution to the specification of the clinical decision support system. **euHeart:** Development of coronary vessel extraction methods from CT and MRI data, and constitution of multivariate database for CRT optimisation.	
Key Items of Infrastructure and Equipment	TherA-Image is a research platform for image guided therapy and minimally invasive surgery. Supported by Europe Feder, this platform has been implemented by university of Rennes 1 (LTSI) at the cardiac centre of Rennes University Hospital. This experimental environment (OR and Catheter lab) equipped with a high technology support (intra-operative 3D imaging / observations, computer aided endovascular navigation, augmented reality) is especially exploited in the context of valve implantation.	

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN BERLIN-BUCH IN DER HELMHOLTZ-GEMEINSCHAFT K.V.	**Max Delbrück Center for Molecular Medicine Berlin**	**7: MDC**
General Description	The **Max Delbrück Center for Molecular Medicine** is a major biomedical research institute within the Helmholtz Association and was recently ranked 16th worldwide (Thomson & Reuters, Cell Biology Institutes), the only German centre to make the top 20 institutions. MDC is the leading Helmholtz centre for cardiovascular research and the leading institute of the recently founded DZHK, the new primary structure for cardiovascular research in Germany. In 2009 and 2013, the MDC's cardiovascular and metabolic research was rated 'outstanding' by an international expert panel. Major state-of-the-art technologies established at the MDC include high-throughput genomic analyses, microscopic imaging, magnetic resonance imaging, the generation, breeding and phenotyping of genetically modified rat and mouse models. The MDC has with the groups Wolf and Falcke and the Berlin Institute of Medical Systems Biology strong research in mathematical modelling. Students can participate in teaching and training of the International Helmholtz Research School 'Translational Cardiovascular and Metabolic Medicine' (TransCard). The MDC has state of the art high performance compute capacity, which will be used for cell simulations.	
Main tasks, match to profile	The **MDC** will provide the proteomic data from patient samples for the whole consortium, and detailed cellular mathematical models for and simulations of excitation-contraction coupling parameterised by the proteomic data.	
Role and Commitment of key people	**Prof. Dr. Martin Falcke** will be the principal investigator coordinating proteomic analysis and cellular simulations of excitation-contraction coupling and their integration into other model components.	
Relevant Publications and/or Research / Innovation Products (Max 5)	K. Thurley, S. C. Tovey, G. Moenke, V. L. Prince, A. Meena, A. P. Thomas, A. Skupin, C. W. Taylor, M. Falcke, Reliable Encoding of Stimulus Intensities Within Random Sequences of Intracellular Ca^{2+} Spikes. *Science Signal.* **7**, ra59- (2014). S. Rüdiger, J. W. Shuai, W. Huisinga, Ch. Nagaiah, G.Warnecke, I. Parker, and M. Falcke, Hybrid Stochastic and Deterministic Simulations of Calcium Blips, Biophys. J. 93 (2007), no. 6, 1847-1857. Ch. Nagaiah, S. Rüdiger, G. Warnecke, and M. Falcke, Adaptive numerical simulation of intracellular calcium dynamics using domain decomposition methods, Applied Numerical Mathematics 58 (2008), 1658-1674. T. Schendel and M. Falcke, Efficient and detailed model of the local Ca^{2+} release unit in the ventricular cardiac myocyte, Genome Informatics 22 (2009), 142-155. T. Schendel, R. Thul, J. Sneyd, and M. Falcke, How does the ryanodine receptor in the ventricular myocyte wake up - by a single or by multiple open L-type Ca^{2+} channels? European Biophysical Journal 41 (2012), 27-39.	
Relevant Previous Projects (Max 5)	**German BMBF eMed initiative SMART:** Applies a multi-scale modelling framework for "quantitative prediction" of treatment outcome **German DFG grant to M. Falcke and G. Warnecke in applied mathematics:** Develops numerical tools and algorithms for 3D myocyte simulations.	
Key Items of Infrastructure and Equipment	Compute cluster and mass spec facility for proteomic analysis.	

	Philips Research Eindhoven	8: PEN
General Description	Royal Philips is a diversified health and well-being company, focused on improving people's lives through meaningful innovation in the areas of Healthcare, Consumer Lifestyle and Lighting. Headquartered in the Netherlands, Philips posted 2013 sales of EUR 23.3 billion and employs approximately 115,000 employees with sales and services in more than 100 countries. The company is a leader in cardiac care, acute care and home healthcare, energy efficient lighting solutions and new lighting applications, as well as male shaving and grooming and oral healthcare. The Global Research Organisation plays an important role in innovation and produces more than half of the patents that Philips files. R&D activities of Philips Research have led to the publishing of thousands of technical and scientific papers. In terms of publications, Philips ranks 4th among Europe's most important and actively publishing research institutions. In Europe, 4 labs employ about 1250 people. More than half of these people work in the Dutch Philips Research Laboratory, which is part of the High Tech Campus in Eindhoven. The Chronic Disease Management department of Philips Research, Eindhoven is composed of 51, mainly post-doctoral, scientists and performs research in the areas of clinical and home healthcare applications and in particular on care planning and management and on telehealth. This group has expertise in machine learning, reasoning and decision support technologies.	
Main tasks, match to profile	Philips Research Eindhoven will provide a software module, based on machine learning and on clinical knowledge obtained from the literature, to infer data that is not available but required for using computational, physiological models for personalised valve disease decision support.	
Role and Commitment of key people	**Dr. Herman ter Horst** is Principal Scientist and works on decision support in healthcare applications with special focus on algorithms that realize machine learning and knowledge representation and reasoning. He has been working on this topic in Philips-internal projects and also in European projects, in particular in VPH-Share and HeartCycle.	
Relevant Publications and/or Research / Innovation Products (Max 5)	• Caffarel, J.; Bescos, C.; Bonomi, A.; Ter Horst, H.; Bover, R.; Cowburn, P.; Squire, I.; Zugck, C.; Cleland, J.; Schauerte, P. (2010). *Clinicians' ability to detect upcoming decompensations in patients with heart failure based on home telemonitoring data.* European Journal of Heart Failure (2013) 15 (S1), S9 • Ter Horst, H.; Sinytsin, A.; *Structuring reasoning for interpretation of sensor data in home-based health and well-being monitoring applications (2012).* Journal of Ambient Intelligence and Smart Environments 4 (2012) 461–476 • Ter Horst, H.; *Combining RDF and part of OWL with rules: semantics, decidability, complexity (2005)*. International Semantic Web Conference 2005, Springer Lecture Notes in Computer Science 3729, pp. 668-684. • Ter Horst, H.; *Completeness, decidability and complexity of entailment for RDF Schema and a semantic extension involving the OWL vocabulary (2005)*. Journal of Web Semantics, 3 (2005) 79-115.	
Relevant Previous Projects (Max 5)	**HeartCycle:** The project developed closed-loop disease management solutions serving heart failure and coronary artery disease patients using monitoring of vital signs and other patient data and providing decision support using machine learning and knowledge-based reasoning technologies; Philips Research Eindhoven was coordinator of HeartCycle. **VPH-Share:** In this project Philips Research, Eindhoven developed data inference algorithms, in particular for enabling application of decision support algorithms even though some input data is missing. In this project Philips Research, Eindhoven also worked on enabling a more integrated view of the status of patients through the provision of data from PHRs (Personal Health Records).	
Key Items of Infrastructure and Equipment		

	Philips Research Hamburg	9: PHILIPS
General Description	Royal Philips is a diversified health and well-being company, focused on improving people's lives through meaningful innovation in the areas of Healthcare, Consumer Lifestyle and Lighting. Headquartered in the Netherlands, Philips posted 2013 sales of EUR 23.3 billion and employs approximately 115,000 employees with sales and services in more than 100 countries. The company is a leader in cardiac care, acute care and home healthcare, energy efficient lighting solutions and new lighting applications, as well as male shaving and grooming and oral healthcare. The Global Research Organisation plays an important role in innovation and produces more than half of the patents that Philips files. R&D activities of Philips Research have led to the publishing of thousands of technical and scientific papers. In terms of publications, Philips ranks 4th among Europe's most important and actively publishing research institutions. In Europe, 4 labs employ about 1250 people. The German Philips Research Laboratory is based in Hamburg and counts about 100 employees, focused in the healthcare area. Its Digital Imaging department is composed of 58, mainly post-doctoral, scientists and performs research in the areas of X-ray imaging physics, image processing for all major modalities (CT/ MR/ US/ X-ray/ NM) and development of new applications covering diagnosis and treatment in cardiology, oncology and neurology. A specific technology developed in this group with a number of important commercial applications is model-based segmentation.	
Main tasks, match to profile	Philips Research Hamburg will provide model and software to compute biomarkers relevant for valve disease that are the basis for patient specific simulations.	
Role and Commitment of key people	**Dr. Irina Waechter-Stehle** is Senior Scientist, works on medical image analysis topics with a specific focus on model-based segmentation and responsible for a Philips-internal project on cardiac US segmentation. In particular, she has experience with the segmentation of valves in CT and US images and will contribute to the image segmentation related tasks in EurValve. **Dr. Jürgen Weese** is Research Fellow and was overall coordinator of euHeart. He works on medical image analysis related topics and is responsible for several Philips-internal projects. He will contribute to the image segmentation related tasks in EurValve.	
Relevant Publications and/or Research / Innovation Products (Max 5)	• Wächter, I.; Kneser, R.; Korosoglou, G.; Peters, J.; Bakker, N.; v. d. Boomen, R.; Weese, J. (2010). *Patient specific models for planning and guidance of minimally invasive aortic valve implantation. Proc.* Miccai 2010, LNCS 6361:526-533. • Ecabert, O.; Peters, J.; Walker, M.J.; Ivanc, T.; Lorenz, C.; von Berg, J.; Lessick, J.; Vembar, M.; Weese, J. (2011) Segmentation of the heart and great vessels in CT images using a model-based adaptation framework, Med Image Anal 15(6):863-876 • Korosoglou, G.; Gitsioudis, G.; Waechter-Stehle, I. et al. (2013) . *Objective quantification of aortic valvular structures by cardiac computed tomography angiography in patients considered for transcatheter aortic valve implantation.* Catheterisation and Cardiovascular Interventions, 81(1), 148-159. • Weese, J.; Groth, A.; Nickisch, H. et al (2013). *Generating anatomical models of the heart and the aorta from medical images for personalised physiological simulations*. Med Biol Eng Comp, 51(11), 1209-1219. • Peters,J.; Lungu,A.; Weber,F.M.; Waechter-Stehle,I.; Hose,D.R.; Weese,J. (2014). *Comparison of CFD-Based and Bernoulli-Based Pressure Drop Estimates across the Aortic Valve Enabled by Shape-Constrained Deformable Segmentation of Cardiac CT Images*, Proc. ISBMS 2014, LNCS 8789:211-219.	
Relevant Previous Projects (Max 5)	**euHeart**: Largest single Integrated Project (16.9M€) in domain of Virtual Physiological Human; developed models and tools for analysis of cardiac and cardiovascular systems; Philips Research Hamburg was coordinator of euHeart. **VP2HF:** The project aims to derive indices for optimal patient-specific treatment selection and planning in Heart Failure via computer models with a focus on CRT. **"NRW Heart Valve Initiative"**: The project focused on the development of a transluminal implantable aortic valve prostheses made of polyurethane and the guidance of transcatheter aortic valve implantation using multiple, complementary imaging modalities.	
Key Items of Infrastructure and Equipment		

Sheffield Teaching Hospitals NHS Foundation Trust	**Sheffield Teaching Hospitals NHS Foundation Trust**	**10: STHFT**
General Description	**Sheffield Teaching Hospital NHS Foundation Trust** (STHFT) manages the five NHS adult hospitals in Sheffield. It provides around one million appointments and operations a year and offers almost every kind of treatment available through the NHS. The majority of our patients are from Sheffield and the surrounding areas but around five per cent of our patients are from other parts of the country. They come to us for specialist treatments, many of which are offered in only a few NHS trusts in the UK. It is also a major employer of local people. Over 13,500 people work at our hospitals in more than 70 professions and a massive variety of jobs, making us the second largest employer in Sheffield. In 2008/09 our turnover is £735m. We work very closely with the University of Sheffield and Sheffield Hallam University to ensure we are at the cutting edge of medical research and development. This helps us to develop new and specialist services for the benefit of patients from Sheffield and all over the country.	
Main tasks, match to profile	STHFT has two core roles, first to develop the data management platform for the project, and second as a clinical partner collecting data for analysis.	
Role and Commitment of key people	**Norman Briffa** is a Consultant Cardiac Surgeon at the South Yorkshire Cardiothoracic Centre. He has an interest in heart valve disease and is one of three mitral valve specialists in the unit. He has set up the postoperative heart valve clinic in Sheffield. He sits on the executive of the British Heart Valve Society. **Steven Wood** is a registered Clinical Scientist and head of the Scientific Computing section of Medical Physics at Sheffield Teaching Hospitals NHS Foundation Trust. Dr Wood has over 11 years' experience, since leaving academia, in the development of clinical software systems across the hospital and is the research informatics lead for the trust. Dr Wood is a member of the INSIGNEO Institute for *in-silico* Medicine, a joint initiative between USFD and the Sheffield Teaching Hospitals Foundation Trust to realise the scientific ambition behind the Virtual Physiological Human (VPH), producing a transformational impact on healthcare. He is also the data management work package leader for the VPH-Share project and overall technical architect for the project.	
Relevant Publications and/or Research / Innovation Products (Max 5)	Rowe R, Iqbal J, Murali-Krishnan R, Sultan A, Orme R, Briffa N, Denvir M, Gunn J. Role of frailty assessment in patients undergoing cardiac interventions. Open Heart. 2014 Feb 1;1(1):e000033. doi: 10.1136/openhrt-2013-000033. eCollection 2014. PubMed PMID: 25332792; PubMed Central PMCID: PMC4195918. Rogers CA, Pike K, Campbell H, Reeves BC, Angelini GD, Gray A, Altman DG, Miller H, Wells S, Taggart DP; CRISP investigators. Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery: a randomised controlled trial (the CRISP trial). Health Technol Assess. 2014 Jul;18(44):v-xx, 1-157. doi: 10.3310/hta18440. PubMed PMID: 25023641. Briffa N. Putting a stop to preventable deaths. Health Serv J. 2013 Aug 23;123(6364):21-3. PubMed PMID: 24199346. Weese, J., Groth, A., Nickisch, H., Barschdorf, H., Weber, F. M., Velut, J., Hose, D. R. (2013). *Generating anatomical models of the heart and the aorta from medical images for personalised physiological simulations*. Med Biol Eng Comp. Brown, A. G., Shi, Y., Marzo, A., Staicu, C., Valverde, I., Beerbaum, P., Lawford P.V., Hose, D. R. (2012). *Accuracy vs. computational time: translating aortic simulations to the clinic*. J Biomech, 45(3), 516-523. Smith, N., de Vecchi, A., McCormick, M., Nordsletten, D., Camara, O., Frangi, A. F., Hose D.R., Rezavi, R. (2011). *euHeart: personalised and integrated cardiac care using patient-specific cardiovascular modelling*. INTERFACE FOCUS, 1(3), 349-364. Shi, Y., Lawford, P., & Hose, R. (2011). *Review of zero-D and 1-D models of blood flow in the cardiovascular system*. Biomed Eng Online, 10, 33. Hose, D. R., Narracott, A. J., Penrose, J. M., Baguley, D., Jones, I. P., Lawford, P. V. (2006). *Fundamental mechanics of aortic heart valve closure*. J Biomech, 39(5), 958-967.	
Relevant Previous Projects (Max 5)	**VPH-Share**: WP Leader and architect of 14.4M€ Integrated Project developed computational infrastructure for data handling and model execution. Developed and deployed model sensitivity analysis tools. **VPH-Dare**: Data infrastructure lead for the 18.1M€ Integrated project investigating the causes of Dementia. **MD-Paedigree**: Data integration partner for the 16.4M€ Integrated project dedicated to constructing and international repository for paediatric data.	
Key Items of Infrastructure and Equipment	Insigneo Institute for In Silico medicine, formal collaboration between University and Sheffield Teaching Hospitals Foundation Trust. Computational and data infrastructures.	

Therenva	**Therenva**	**11: THERENVA**
General Description	**Therenva SAS** is a French SME founded late 2007 as a spin-off of the LTSI academic research lab (Inserm, French National Institute for Health). With a staff of 10 people, mostly engineers specialised in image processing, and a strong focus on the clinician user experience, Therenva designs medical device software systems for minimally-invasive cardiovascular interventions. Therenva develops and markets : - the leading endovascular case planning software EndoSize® (CE-marked and FDA-approved) providing surgeons and cardiologists with an efficient tool for choosing the optimal procedure strategy and implant device based on patient CT images; - the intraoperative navigation system EndoNaut®, providing ergonomic image fusion tools and 3D endovascular device localisation capabilities to the physician in standard operating rooms. Therenva has developed strong clinical and academic partnerships, especially with the Cardiovascular Surgery Department of the University Hospital of Rennes, a French leading cardiovascular centre.	
Main tasks, match to profile	Therenva will lead the DSS workpackage and will develop the clinical DSS software resulting from this project.	
Role and Commitment of key people	**Cemil Göksu** graduated from the Ecole Centrale de Lyon where he obtained an engineering degree and a Master's degree specialising in Bioengineering and Medical Imaging in 2001. He joined the Image and Signal Processing Laboratory (LTSI Inserm U642) as a PhD student from 2001 to 2005. His research activities contributed to the design and development of an image-guided system for endovascular surgery. Since 2007, he is the co-founder and CEO of Therenva, awarded by the French Ministry of Research at the 2007 Innovative Startup Contest and first prize winner of the 2008 AGBM Innovative Medical Device Technology Award.	
Relevant Publications and/or Research / Innovation Products (Max 5)	Dumenil et al., Finite-Element-Based Matching of Pre- and Intraoperative Data for Image-Guided Endovascular Aneurysm Repair, IEEE Transactions on Biomedical Engineering, 60, no 5 (2013): 1353 62. Adrien Kaladji et al., Prediction of deformations during endovascular aortic aneurysm repair using finite element simulation, Special Issue on Mixed Reality Guidance of Therapy - Towards Clinical Implementation 37, no 2 (2013): 142 49.	
Relevant Previous Projects (Max 5)	**MEDIATE** (EU project): ITEA Award of Excellence in the category Business impact **ANGIOVISION** (French ANR collaborative project)	
Key Items of Infrastructure and Equipment	Access to a research hybrid OR for 3D acquisition	

	Eindhoven University of Technology	12: TU/e
General Description	Eindhoven University of Technology (TU/e) is a research university specializing in engineering science & technology. Education, research, and knowledge exploitation contribute to: • Science for society: solving the major societal issues and boosting prosperity and welfare by focusing on the Strategic Areas of Energy, Smart Mobility, and Health. • Science for industry: the development of technological innovation in cooperation with industry • Science for science: progress in engineering sciences through excellence in key research cores and innovation in education TU/e is a leading university offering excellent teaching and research, contributing to the advancement of engineering sciences and research to the developing of technological innovations and the growth of wealth. To ensure that research responds flexibly to dynamic external developments and to strengthen the societal and economic impact of the research, TU/e concentrates on strategic areas around the major societal issues, Energy, Smart Mobility, and Health, and emphasises knowledge utilisation: research results translated into innovations serve as a basis for creating new products, processes and enterprises. TU/e has over 8000 students (5000 BSc, 3000 MSc) and over 2000 research staff and 800 PhD students. TU/e is also one of the first universities in Europe with a Department of Biomedical Engineering with a dedicated and complete undergraduate and graduate program. The Cardiovascular Biomechanics (CVB) group of the Department of Biomedical Engineering focuses on numerical and experimental modelling of the cardiovascular system, with the aim to improve and develop diagnostic methods and therapeutic protocols. Special attention is given to the complex constitutive behaviour of biological tissues, including their ability to adapt to changing environment. In addition to computational studies, ex vivo experimental techniques that enable temporary cultivation of animal arterial segments and hearts are developed. The group has built ample experience in including sensitivity and uncertainty analysis to enable patient specific model predictive clinical decision support applications. In this proposal it is envisioned that these sensitivity and uncertainty analysis be employed in EurValve.	
Tasks/Profile	Provision and deployment of software tools that perform variation and sensitivity analysis.	
Role and Commitment of key people	**Prof. dr. ir. Frans van de Vosse** (male), FTE (10%) is graduated in physics and professor of Cardiovascular Biomechanics at the Eindhoven University of Technology and honorary professor of Cardiovascular Biomechanics at Maastricht University Medical Centre. He is specialised in computational fluid dynamics and fluid structure interaction, experimental verification, and cardiovascular physiology. Current research relates to the computational and experimental biomechanical analysis of the cardiovascular system and its application to clinical diagnosis and intervention. To advance the translation of research to the clinic he initiated and cofounded the School of Medical Physics and Engineering (SMPE/e). He initiated and supervised a number of national and international projects or project work packages on the interface between technological and clinical research including EU-funded projects in FP6, Eureka and FP7. He has (co-)supervised more than 30 PhD students and is (co-)author of over 120 scientific publications in internationally refereed technological as well as clinical journals (h-index 26).	
Relevant Publications and/or Research / Innovation Products (Max 5)	• Huberts, W., Donders, W.P., Delhaas, T. & Vosse, F.N. van de (2014). Applicability of the polynomial chaos expansion method for personalization of a cardiovascular pulse wave propagation model. International Journal for Numerical Methods in Biomedical Engineering, 30(12), 1679-1704 • Caroli, A., Manini, S., Antiga, L., Passera, K., Ene-Iiodache, B., Rota, S., Remuzzi, G., Bode, A.S., Leermakers, J., Vosse, F.N. van de, Vanholder, R., Malovrh, M., Tordoir, J. & Remuzzi, A. (2013). Validation of a patient-specific hemodynamic computational model for surgical planning of vascular access in hemodialysis patients. Kidney International, 84, 1237-1245. • Horst, A. van der, Boogaard, F.L., Veer, M. van 't, Rutten, M.C.M., Pijls, N.H.J. & Vosse, F.N. van de (2013). Towards patient-specific modeling of coronary hemodynamics in healthy and diseased state. Computational and Mathematical Methods in Medicine, 2013, 393792-1/15 • Vosse, F.N. van de & Stergiopulos, N. (2011). Pulse Wave Propagation in the Arterial Tree. Annual Review of Fluid Mechanics, 43, 467-499. • Loon, R. van, Anderson, P.D. & Vosse, F.N. van de (2006). A fluid-structure interaction method with solid-rigid contact for heart valve dynamics. Journal of Computational Physics, 217(2), 806-823 • Loon, R. van, Anderson, P.D., Baaijens, F.P.T. & Vosse, F.N. van de (2005). A three-dimensional fluid–structure interaction method for heart valve modelling. Comptes Rendus Mecanique, 333(12), 856-866	
Relevant Previous Projects (Max 5)	**VPH-Share**: Use-case on sensitivity and uncertainty analysis for coronary artery disease. **ARCH**: Computational infrastructure for surgical decision support including sensitivity and uncertainty analysis tools **MeDDiCA**: Project educating researchers in the field of cardiovascular medical devices and contributing to enhanced knowledge and skills in the field of cardiovascular health care **Discipulus**: Roadmap for the Digital Patient main editor of a chapter on clinical data	
Equipment	Computational infrastructures.	

University of Bristol	13: UBRIS

General Description	The **University of Bristol (UBRIS)** is a member of the UK's prestigious "Russell Group" of research-intensive institutions. In the UK's recent nationwide audit of research it was ranked fourth in the UK for the combination of quality and volume of its research activity. Bristol is the lead partner in SPHERE, a UK flagship Healthcare Technology research grant, developing an integrated platform of sensors and the requisite data analysis capability for long term pervasive health applications. Prof Craddock is the Director of SPHERE and Dr Piechocki leads the wearable sensor development, targeting ultra-low power operation n harvested power and seamless connectivity for greater usability in ling term clinical and research scenarios. Bristol's Intelligent Systems Laboratory (ISL) is known for world-leading research contributions in machine learning and data mining theory (including kernel methods, various approaches to data fusion, exploratory data mining) as well as for the successful application of this theoretical expertise in collaboration with scientists in other data-driven projects (including SPHERE but also projects in bioinformatics, social media analysis, music informatics, and finance). Dr De Bie from the ISL contributes his expertise in machine learning and the analysis of time-series data to this proposal.
Main tasks, match to profile	UBRIS will provide the sensor systems used in the project (work package 4) and provide algorithms to make sense or this data.
Role and Commitment of key people	**Prof Ian Craddock** is Director of the SPHERE project, co-ordinating a programme of research spanning wearable activity recognition, video analytics, low power communications, energy harvesting and machine learning. He also undertaking pioneering interdisciplinary research in medical imaging; he founded a company that has attracted investment of £4M to undertake clinical trials and commercialise a cancer imaging device. He serves on the Steering Board of the University's flagship Elizabeth Blackwell Health Research Institute. **Dr Tijl De Bie** has his primary expertise in machine learning and data mining with a particular focus on data fusion, semi-supervised learning, and structured data (including sequence and time series data), as well as in applications ranging from music informatics over social media mining to computational biology. Since May 2014 he is holder of the ERC Consolidator Grant FORSIED on the theoretical foundations of exploratory data mining. Dr De Bie will provide input on the machine learning and data fusion aspects of the project, including feature and algorithm design for activity recognition and the quantification of activity levels. **Dr Rob Piechocki** has in-depth expertise in Advanced Wireless systems. His interests span: Statistical Signal Processing, Information and Communication Theory, Internet of Things, Ultra Low Power Wearables and Communications; and Vehicular Communications. He has published over 100 papers in journals and conferences in these areas. He is currently leading the development of Wireless Sensing and Communications technologies part of SHPERE project.
Relevant Publications and/or Research / Innovation Products (Max 5)	1. G. R. G. Lanckriet, T De Bie, N. Cristianini, M. I. Jordan, and W. Stafford Noble "A statistical framework for genomic data fusion." Bioinformatics (2004) 20 (16): 2626-2635 2. E. Ricci, T. De Bie, and N. Cristianini. "Magic moments for structured output prediction." Journal of Machine Learning Research 9.12 (2008). 3. P Woznowski, R Piechocki, D Kaleshi, I Craddock, et al "A Multi-modal Sensor Infrastructure for Healthcare in a Residential Environment" IEEE International Conference on Communications, London, June 2015. 4. S-E Adami, P P Proynov, B H Stark, G S Hilton and I J Craddock, "Experimental Study of RF Energy Transfer System in Indoor Environment", Journal of Physics Conf Series, volume 557, 012005, 2014. 5. X Fafoutis, E Mellios, G Hilton, R Piechocki, I Craddock, "Towards an Ultra Low-Power Long-Term Activity Monitoring System for Healthcare Applications" IEEE Systems Journal: "Communications Technologies and Infrastructures for Smart eHealth Systems (under review).
Relevant Previous Projects (Max 5)	**SPHERE** a UK flagship health technology project, developing a multi-sensor approach to activity recognition and measurement. SPHERE comprises 60 researchers and has a total budget approaching €20M, from the UK government and industry. MRC **Integrative Epidemiology Unit (IEU)**, a €32M centre applying novel causal methods to key research questions related to causes of bone, cardiometabolic, reproductive, mental and other aspects of ill-health. The IEU's Data Capture theme, led by Prof Craddock, is currently commencing deployment of SPHERE's wearable sensors within a cohort of pregnant women. **TOMMORROW**, an industry-funded trial aiming to assess whether certain genes predict the risk of conversion from healthy ageing to mild cognitive impairment and whether a drug, pioglitazone, will delay the progression. **RADAR,** a €3M grant from NIHR to fund a clinical trial of losartan as a disease modifying agent in Alzheimer's disease; Bristol are the lead site recruiting for RADAR which is opening in 20 centres around the UK.
Key Items of Infrastructure and Equipment	SPHERE's house in a residential street in central Bristol is equipped as a unique test bed for deployment of domestic sensing technology, facilitating the rapid development of usable, reliable, sensors for this project.

4.2 Third parties involved in the project (including use of third party resources)

No third parties involved.

Subcontracting

Except for the use of external auditors by some beneficiaries, no subcontractors are involved.

5. Ethics and Security

5.1 Ethics

EurValve is an ICT Research and Innovation project targeting the 'Health, Demographic Change and Wellbeing Challenge, under Personalising Health and Care'. EurValve will implement, test and validate a modelling decision support system (DSS) for aortic and mitral valve diseases that allows simulation, comparison and risk stratification of different treatment strategies, resulting in an improved understanding of the effects of treatment (outcomes). In addition, the DSS will improve our knowledge of disease mechanisms by applying a holistic assessment of cardiovascular function and couples organ function with cellular function.

The partners of EurValve are committed to carrying out this research '*in compliance with ethical principles (including the highest standards of research integrity*' as set out in the European Code of Conduct for Research Integrity '*including, avoiding fabrication, falsification, plagiarism or other research misconduct) and, with EU and national law*'.

Table 6: Ethical Issues

	YES	NO
Informed Consent		
Does the proposal involve children?		X
Does the proposal involve patients or persons not able to give consent?		X
Does the proposal involve adult healthy volunteers?		X
Does the proposal involve Human Genetic Material?		X
Does the proposal involve Human biological samples?	X	
Does the proposal involve Human data collection?	X	
Research on Human embryo/foetus		
Does the proposal involve Human Embryos?		X
Does the proposal involve Human Foetal Tissue / Cells?		X
Does the proposal involve Human Embryonic Stem Cells?		X
Privacy		
Does the proposal involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)	X	
Does the proposal involve tracking the location or observation of people?		X
Research on Animals		
Does the proposal involve research on animals?		X
Are those animals transgenic small laboratory animals?		X
Are those animals transgenic farm animals?		X
Are those animals cloned farm animals?		X
Are those animals non-human primates?		X
Research Involving Developing Countries		
Use of local resources (genetic, animal, plant etc)		X
Benefit to local community (capacity building i.e. access to healthcare, education etc)		X
Dual Use		**X**
Research having direct military application		X
Research having the potential for terrorist abuse		X
ICT Implants		
Does the proposal involve clinical trials of ICT implants?		X
I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL		**X**

As indicated in Table 6 above, the ethical issues identified within EurValve relate to the ***use of human biological samples*** and the *collection of* ***human data***. Since the project involves the processing of personal data related to patient health, ***privacy*** must also be ensured. These are the focus of the EurValve ethics self-assessment presented below;

Ethics Self-Assessment

The information provided to fulfil the ethics self-assessment for EurValve is divided into 3 subsections:

- Justification of the ***requirement*** for access to human data and tissue samples and the types of personal data and tissue samples that will be obtained in the course of the EurValve project.
- The ***sources*** of these data/tissues and the ***processes and safe-guards*** that will be actioned in order to ensure that appropriate ethical approvals are put in place and that data and sample collection, storage and use are ethical and compliant with the applicable European and national legislation.
- An ***overview*** of the ***current relevant legislative*** landscape within the EU and at the national level that will apply to this project.

5.1.1 Justification of requirement for access to human data and tissue samples;

In order to meet its objectives EurValve will require access to patient-specific clinical data (both retrospective and prospective) including pre-treatment and follow-up data, activity data and myocardial tissue samples from patients suffering from valvular heart disease. The clinical problem addressed and the potential outputs of the work plan are detailed in Sections 1 and 2 of the proposal.

Subsets of these data are variously required to support tasks associated with;

- **WP2 & WP6** -population and augmentation of the data warehouse;
- **WP6** - for the operation of the machine learning tools for the development of new knowledge;
- **WP4** – for the development of methods for the interpretation of activity data and,
- **WP6** for the evaluation of the operation of the DSS at the clinical centres.
  This task will require access to a small library of patient-specific data (including images obtained both pre and post-intervention).
- Myocardial biopsies will be obtained for the purpose of analysing proteomic information. These data will be required **for WP3**.

5.1.2 Source of patient data/tissue samples.

The partners of EurValve are cognisant of the issues associated with the use of personal health-related data, mindful of their ethical responsibilities in the conduct of medical research and the requirement to ensure that the needs and expectations of society are taken into account. In no case and under no circumstances will research activity involving ethically sensitive issues be started before the proper local authorisation is given, according to the national law where the activities will be conducted and taking account of all applicable EU legislation.

The ethical and data protection issues which relate to data access during the project are summarised below and the intended sources and types of clinical data and tissue samples are identified together with their current status and the steps that will be needed in order to comply local and European ethical and governance requirements.

The ambition of EurValve is to integrate all available patient data to develop models with a level of personalisation not hitherto achieved and, for this reason, a wide range of data is required. Patient-specific data includes; PACS (image) data (acquired both before and after intervention), physiological data, patient-specific molecular data (derived from the analysis of myocardial tissue biopsies as discussed later), demographic data, information on co-morbidities and other data from the Electronic Health Record Data. Patient record data are potentially highly sensitive and their secondary use for research purposes raises both ethical and data protection issues. Disclosure of patient data could cause serious problems for the medical profession and be potentially damaging to individual patients and clinicians. Yet at the same time patient records are a hugely valuable resource in terms of clinical research and patient treatment.

With the exception of molecular data and activity monitoring all data that EurValve will seek to access will be that collected routinely in the course of the patient's normal clinical pathway.

In all cases, the ethics process for collection of personal data will be managed by the relevant clinical centre.

Clinical data will be provided by the three clinical partners in EurValve, namely;

- The Catharina Hospital, Eindhoven, the Netherlands, (CATH)
- The German Heart Institute, Berlin, Germany (DHZB)
- The Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK (STHFT)

Subject to favourable ethical approval, the majority of data will be collected prospectively through activities outlined in WP4. A requirement within the study protocol that data be collected not only prior to treatment but also at clinical follow-up means that the data cannot be rendered non-identifiable but will be pseudonymised the clinical centre before being accessed by the project.

Access to retrospective data would benefit developments in the earlier stages of the project. This includes data employed in context of the development and testing of the ICT environment. As there is no requirement for prospective collection for this purpose, the data could be rendered non-identifiable. Through the activities of partners DHZB and STHFT the project has already established that some data is available for use if they meet the local governance requirements at the respective centres and, from experience, we do not foresee any barriers to these conditions being met. These data are identified under the partner-specific discussions below, together with a summary of their current ethical status with respect to research use and data-sharing.

In addition to access to routine clinical data, favourable ethical approval will be sought to carry out pervasive activity monitoring for a small sub-cohort of patients.

Human Tissue Samples: Myocardial biopsies will be obtained for the purpose of analysing proteomic information. Samples will be taken at the time of surgery from patients recruited to the study at DHZB. Samples will be transferred to partner MDC for analysis based on local governance and research agreements between DHZB and MDC.

5.1.3 Overview of Ethical Landscape

There follows a discussion of the key elements of the ethical landscape that will apply to EurValve.

5.1.3.1 Use of Patient Data

A key aspect of any research and development project is to protect the interests of users and participants. In this regard, the use of patient data and the related issues of confidentiality and privacy in EurValve requires particular attention. While there will be absolutely no risk of physical harm for any patient whose data may become used for this research, it is important that the work is carried out to strict ethical standards in relation to user privacy, confidentiality and consent.

The consortium is fully aware of the privacy and data protection issues involved in this project and has consulted the Data Protection Directive (Directive 95/46/EC) and the Data Protection Working Party paper, adopted on February 15th 2007 concerning the processing of personal data relating to health in electronic health records (00323/07/EN WP 131).

Furthermore, to indeed realise access to a clearly defined and delimited set of data required for the research, formal procedures for approval of such access will be initiated. This will be undertaken via the respective ethics committees and, if required, the relevant regional or national health/scientific ethics committees. Specific national regulations and laws will, of course, equally be consulted and adhered to.

In the context of collection of clinical and biological information, the project has been developed according to The Charter of Fundamental Rights of the European Union (Nice, 2000), the Declaration of Helsinki: Recommendation For Conduct of Clinical Research (Helsinki, 1964; revised in Hong Kong, 1989), and the Convention of the Council of Europe on Human Rights and Biomedicine (Oviedo, 1997). Research operations were designed with reference to with the European Union Directive 2001/20/EC (Good Clinical Practice in the conduct of clinical trials on medicinal products for human use), Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and the European Union Directive 95/46/EC (on the processing and free movement of personal data).

It is not envisaged that data or tissue will be shared with any third party during the duration of EurValve. Data shared within the project will be pseudonymised or, whenever feasible, rendered non-identifiable. No sensitive personal data will be collected or processed by the project. Activity monitoring will be restricted to the use of accelerometers/ motion sensors.

5.1.3.2 Patient consent, autonomy and anonymisation

The concept of autonomy is intimately tied up with the legal duties of consent and confidentiality. For projects such as EurValve one of the key ethical issues will be in the possible compromise of the patient's autonomy that will arise from sharing his or her data beyond the clinical care team. The European Article 29 Data Protection Working Party has argued that consent may have only a very limited place as a justification of the sharing of health related data in the electronic age.

The limitation is based on the argument that to exercise autonomy a patient must be able to make decisions unfettered by coercion. If it is accepted that sharing health data allows doctors to provide better care, then 'a patient who refuses permission to share such information will be de facto opting for a lower quality of healthcare, arguable therefore he or she is not able to withhold consent freely and is therefore not able to act autonomously.' It is argued therefore that robust system of security of information and ethical practice should be adopted in which patients will be able to trust, notwithstanding that their information is shared, and providing for special opt-out possibilities when the nature of the information is especially sensitive.

In more practical terms, in the core of the doctrine of informed consent commonly stands the principle that any preventive, diagnostic or therapeutic medical intervention as well as scientific research involving human subjects is only acceptable with ***the prior, free and informed consent*** of the person concerned, based on adequate information. Furthermore, consent should, where appropriate, be expressed and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice.

According to international standards, informed consent is required for collecting, storing, and using human biological material such as tissue, blood, or DNA and data processed from tissue. This requirement is based on the ethical principle of autonomy. In the European Union, a framework of data protection rules also obligates researchers to obtain consent to data processing and storage.

Participation of persons providing personal data must be entirely voluntary and for all prospective data collected, unless rendered non-identifiable, ***informed consent will be obtained in advance and clearly documented***.

Participants will be provided with an 'informed consent form' and detailed 'patient information sheets' that:

- Are in a language and in terms fully understandable to them,
- Describe the aims, methods and implications of the research, the nature of the participation and any benefits, risks or discomfort that might be involved,
- Explicitly state that participation is voluntary and that anyone has the right to refuse to participate and to withdraw their participation, samples or data at any time — without any consequences,
- Indicate how biological samples and data will be collected, protected during the project and either destroyed or reused subsequently,

Incidental Findings: In this case the study protocol is in line with the routine diagnostics carried out prior to valve intervention. As a consequence we do not expect incidental findings that would not be found in standard care, meaning that all patients will be informed of the findings.

Children: For the avoidance of doubt, and as indicated in Table 6 above, no children will be included in the research.

Recruitment will be carried out by a member of the clinical care team and every effort will be made to ensure that the potential participant has fully understood the information provided and does not feel pressured or coerced into giving consent. Consent will be given in writing (e.g. by signing the 'informed consent form' and 'information sheets'). Patients who are unable to give consent will not be recruited to the study.

5.1.3.3 Confidentiality and Privacy

Beside the general issues on data treatment posed by any ICT for Health research, VPH research raises some original issues, as discussed at length in the VPH Research Roadmap of the STEP action. In this document it is suggested that all of these issues should be analysed in the context of the relevant European legislation, which will have to be considered and taken into account, including in particular;

- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data,

- and the ARTICLE 29 Data Protection Working Party's working document on the processing of personal data relating to health in electronic health records (EHR) (document 00323/07/EN; WP 131; adopted on 15 February 2007).

The section on 'Use of EHR for other purposes' (p. 16) states that 'processing of EHR-data for the purposes of medical scientific research and government statistics could be allowed as an exception to the rule so as to protect the fundamental rights and the privacy of individuals. Moreover, whenever feasible and possible, data from EHR systems should be used for other purposes (e.g. statistics or quality evaluation) only in anonymised form or at least with secure pseudonymisation.'

The primary problem appears the need for the transfer of potentially sensitive clinical data, from the clinical institution where they are collected, to other institutions where they are processed in order to generate the models predictions or to the digital library service. This is actively addressed in the proposal.

5.1.3.4 Role of Advisory Boards

As outlined in the proposal, EurValve will constitute a Clinical & Ethical Board which will provide oversight for all ethical issues and ensure that robust procedures are in place and that these are handled appropriately across all partners. The CEB will provide a continuing analysis of all relevant national legal and regulatory constraints, and will monitor the respect maintained by each consortium partner for both these and the relevant international reference documents. Board membership will be such as to provide relevant experience and expertise in relation to ethico-legal concerns that might arise from the clinical research activities of the project. The CEB will be committed to promoting best practice in methods of compliance with the ethical principles throughout the project's activities. The CEB will require full transparency in this respect by each partner of the project, so that all possible guarantees are foreseen that the highest clinical & ethical standards will be applied in all research activities which are part of this project. The science and society issues related to the project will be monitored by maintaining a yearly updated general public awareness document on the impact of the novel discoveries produced by the project. Furthermore the CEB will monitor that each participant of the project has the same basic understanding on the ethical and safety issues of the project.

5.1.3.5 Impact of National Regulatory Frameworks

In addition to compliance with European legislation the project must take into account the interpretation of European directives in the relevant Member States. The sections below describe the national regulatory frameworks associated with the three clinical partners. The management of the ethical issues associated with the use of clinical data is reported in accordance with the laws, the regulations and the internal procedures in the various partner institutions and the ethical consent, data protection and governance issues associated with the different datasets.

5.1.3.5.1 The Netherlands

The Netherlands has a robust and transparent Governance Framework. The Central Committee on Research involving Human Subjects (CCMO) publishes core information from the national application form (ABR form) in a public CCMO register. This information covers all WMO studies (ie studies covered by the Medical Research (Human Subjects) Act which gives effect to Directive 2001/20/EC) which have been approved by the accredited medical ethical committees (MRECs) and the CCMO. By means of an Annual Report, the CCMO presents an overview each year of all research that is reviewed in the Netherlands by the accredited MRECs and the CCMO. There are 24 accredited regional (MRECs) that review medical/scientific research proposals. Each is linked to an academic medical centre or hospital. The majority of the MRECs carry out reviews for the whole of the Netherlands but, for the purposes of EurValve, a favourable ethical opinion will be sought from the local MREC in Eindhoven for the use of prospective personal data for this study.

All data provided to EurValve by partner CATH will be collected prospectively under a new ethics submission.

5.1.3.5.2 The UK

In the UK, EU Directive 2001/20/EC is embodied in UK law in the Medicines for Human use (Clinical Trials Regulations) 2004. All research involving patients is approved and monitored through the Research Governance Framework which applies clear national standards. Research Governance embraces five elements: science, information, finance, health and safety, and ethics. Ethical review within the UK is the responsibility of the Research Ethics Service administered through a group of more than 80 research ethics committees (RECs). The UK RECs are legal entities that are accountable to the UK Ethics Committee Authority (UKECA), a body that is accountable to the EU. As in the Netherlands an application can be made to any national REC but in the context

of EurValve, for the prospective collection of personal data needed, .a favourable ethical opinion will be sought from the local (Sheffield) REC.

Data collected prospectively at USFD will require a new ethics submission.

In the UK exceptions are made for some types of research involving the use of retrospective data. These include:

- Research limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection), provided that the patients or service users are **not identifiable** to the research team in carrying out the research.
- Research limited to secondary use of tissue samples previously collected in the course of normal care with consent for research, provided that the patients or service users are **not identifiable** to the research team in carrying out the research as described in the UK health departments' policy document 'Governance arrangement for research ethics committees; a harmonised edition (updated April, 2012) [118, 119]

USFD has identified retrospective imaging data, collected as part of a patient's standard care path, which could be made *available to the project in unidentified form. No REC review is required but local R&D approval will be required.*

5.1.3.5.3 Germany

Whilst the Netherlands and UK have very similar Research Frameworks and ethical procedures, the situation in Germany is quite different with no centralised authority[120].

In Germany there are a total of 53 research ethics committees 33 of which are attached to Faculties of Medicine/Universities, 17 to Medical Associations ("Ärztekammern") in the States and 3 to States governments. The legal competence of the 3 RECs attached to States governments is restricted to drug research and to research on medicinal devices. These RECs are established in conformity with States law and the Federal Republic has no competence for that establishment. EU-Directive 2001/20/EC (4th of August 2004) is embodied in German Law through the 12th Novel Federal Drug Law ("Bundesarzneimittelgesetz"). There is no specific legislation concerning biomedical research which is not covered by the Federal Drug Law and by the Federal Law on Medicinal Devices and up until now Germany has no legislation on biomedical research as a whole. Physicians in Germany have to follow their Medical Assocation's Professional Code of Conduct which becomes a legally binding instrument by a decree of the Federal States governments and can slightly differ among the different Federal States ("Bundesländer").

For studies performed by an investigator attached to a university, the REC of the Faculty of Medicine or of the University can assess the research. Medical researchers are obliged by a code ("Ärztliche Berufsordnung") which, in the German States is a legally binding instrument, and / or by the "Intramural Right" of Universities to submit any biomedical research project to the REC of the Medical Association or of the University/Faculty of Medicine. In contrast to drug research and research on medicinal devices here the decision of the REC is an advice, neither a permission, nor a prohibition. There is no Central REC for the review of individual biomedical research projects.

DHZB has already ensured the approval of the Ethics Committee of the Medical University Berlin to use imaging and proteomics data for patient specific modelling in the area of heart failure and valve disease including biopsies of the left myocardium (approval number EA2/133/14.). **A copy of the approval letter has been provided to the Commission and is appended to this proposal.**

For early evaluation of machine learning aspects DHZB will seek ethical approval for secondary use of existing data. DHZB has access to MR imaging data for app. 20-40 patients with aortic valve replacement (data acquired before and after valve replacement). This data comes from national German and EU FP7 research sources which

[118] http://www.hra.nhs.uk/resources/research-legislation-and-governance/governance-arrangements-for-research-ethics-committees/#sthash.tCnjINIb.dpuf
[119] http://www.hra.nhs.uk/resources/research-legislation-and-governance/governance-arrangements-for-research-ethics-committees/
[120] http://www.eurecnet.org/information/germany.html

have existing favourable ethical opinion for use in valvular heart disease research. The sources of this data are (a) A German Science Foundation; project entitled "Computer assisted surgery in Congenital Heart Diseases"; (b) The EU FP7 project Cardioproof www.Cardioproff.eu.

5.1.3.6 Projected Timeline

Partners STHFT and CATH will apply to their local RECs to seek ethical review for the project and a favourable ethical approval for access to the patient data identified above by PM 6. The clinical partners are well-versed in making such applications and have a good understanding of the processes involved and the supporting information that will be required. In the UK RECs are required to give an ethical opinion within 60 calendar days of the receipt of a valid application. The clinical partners will start to gather the necessary information and develop the protocol, produce Patient Consent Forms and Patient Information Sheets from the outset of the project. The clinical cohort inclusion criteria (due PM 2) and patient inclusion criteria (due PM 4) will be defined concurrently. Every effort will be made to obtain access to high quality prospective data at the earliest opportunity and, for this reason, the ethical submission will focus on the core requirements i.e. images and data obtained as part of the standard clinical care pathway in the first instance with data capture from activity monitoring added as an immediate minor amendment (no data needed until PM12). A favourable ethical opinion is already in place for the collection of myocardial biopsies by DHZB.

Note on Patient Selection: Criteria will be defined as part of the funded research; details on sex, age and ethnicity will become available only after recruitment.

Having already established that data is available, it is anticipated that the lighter-touch approach requiring R&D approval only for access to retrospective data at STHFT should be in place by PM3.

5.1.3.7 Internal approval for access to clinical data within the project

Appropriate internal controls concerning access to patient data by members of the project team in their capacity as researchers in the EurValve project are necessary. Ultimately, before any access to data begins, the project management will need to ensure that appropriate controls are in place to support this access and to prevent or limit possible abuse. Furthermore, all post-processing of clinical data will be coordinated by the project coordinator, in collaboration with the Project Board and Clinical and Ethics Board.

5.1.3.8 Data Storage, Access and Security

The design of the ICT environment for the usage and exchange of patient data, incorporates the material content of the following:

- Directive 95/46/CE of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and free movement of such data as well as
- Convention No. 108 of the Council of Europe for the Protection of Individuals with regard to Automatic Processing of Personal Data adopted on 28 January 1997;
- Recommendation No. R (97) 18 of Committee of Ministers to Member States concerning the protection of personal data collected and processed for statistical purposes, adopted on 30 September 1997;
- Directive 96/9/EC of the European Parliament and the Council of 11 March 1996 on the legal protection of databases
- Directive 2000/31/EC of the European Parliament and of the Council of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market (Directive on Electronic Commerce)
- Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications)

5.1.3.9 Data Security

As discussed in Section 1.5 the ambition of EurValve is to develop a Decision Support System which goes well beyond the state of the art. In other areas of computationally-intensive research, albeit in less security-minded domains, cloud computing has achieved considerable success and cloud providers are taking steps to demonstrate

that data can indeed be stored and processed in a public infrastructure[121]. Based on experience of partners (USFD, CYFRONET) who are fully cognisant of these the robust data security and confidentiality requirements of the medical domain, having played major roles in the VPH-Share EU FP7 project (Grant agreement number: 269978, the platform proposed for EurValve will manage clinical workflow and computational/data services whilst maintaining security and confidentiality.

The medical domain introduces some specific restrictions when dealing with distributed computing systems due the need to ensure security and confidentiality of medical data. In less security minded areas this creates the possibility of deploying the DSS outside the confines of the Medical Institutions using software as a service scenario. Security aspects are one of the most crucial for any IT system operating on medical data and the project partners regard this as a priority. Robust Authentication, Authorisation and Accounting mechanisms are critical to ensuring an adequate level of security. Production of a solution to proper access control will be a target of WP2.

A mechanism is also needed to ensure that data cannot be recovered after deletion using reasonable time and resources. This is an inherent limitation of some physical storage media. If permanent storage is needed all data will be encrypted. A mechanism will be proposed in WP2 for the safe movement of data.

Infrastructure technology (TrialConnect, Telekom Healthcare) has already been developed and used, successfully in former and current EU projects for clinical data management. This technology allows the (pseudo-) anonymisation upload and web-based management of Medical DICOM images, in conjunction with relevant clinical information, into a study database. This platform will be used for all prospective clinical study data acquired in EurValve.

Details of the GCP-compliant data management system to be used for this project will be available soon after project commencement.

[121] Eg Microsoft Azure is claimed to comply with EU Data Protection Directive (95/46/EC) and the corresponding US legislation.

5.1.3.10 Practical Security Measures

All investigators will comply with directive 95/46/EC on the protection of individuals with regard to the processing of personal data, and measures will be taken to ensure data security at study sites.

Non-electronic records

- Research files will be stored in locked filing cabinets in non-public areas
- Files containing information that could identify a study participant will be kept separate from the research files, in separate locked cabinets
- Written evidence of a subject's participation in a study is kept locked when not in use
- Hard-copy machinery is located in staff-only limited-access areas, checked to ensure confidential information is secure

Electronic records

- Records are stored on secure servers, backed-up daily
- Only project-authorised personnel will have data access rights, including data administrator access.
- All sites maintain state-of-the art security of their physical data systems, which include firewalls and virus protection regularly updated.
- Back-up files at the participating institutions are maintained at a separate location to prevent data loss due to fire, theft, or other incident.
- Study staff at each location will only have access to that data which is relevant to their project roles.
- Individual workstations are password protected and access to these machines is physically restricted
- Identifying information will be stored separately from all assessment data.
- Data will be audited on an on-going basis to ensure confidentiality safeguards are being maintained and data integrity is being maintained at each site.

References

- www.esf.org/fileadmin/Public.../Code_Conduct_ResearchIntegrity.pdf
- Department of Health (2005) Research Governance Framework for Health and Social Care. 2nd edn, London, DH. Available www.dh.gov.uk.
- National Research Ethics Service http://www.nres.npsa.nhs.uk/aboutus/
- National Institute for Health Research http://www.nihr.ac.uk/Pages/default.aspx
- WMA Declaration of Helsinki. Available at http://www.wma.net/en/30publications/10policies/b3/
- Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo, 4 April 1997) (Oviedo Bioethics)
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use as well as the requirements for authorization of the manufacturing or importation of such products (OJ L 91, 9.4.2005, p. 13).
- Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC (OJ L158, 27/5/2014).
- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p.48).
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (OJ L 281, 23.11.1995, p. 31)
- News on the revision of Directive 95/46/EC. Available at http://ec.europa.eu/justice/data-protection/index_en.htm.
- Article 29 Working Party Documentation. Available at http://ec.europa.eu/justice/data-protection/article-29/documentation/index_en.htm.H2020 How to complete your ethics self-assessment 22

5.2 Security[122]

Please indicate if your project will involve:

Activities or results raising security issues	~~YES~~/NO
'EU-classified information' as background or results	~~YES~~/NO

End

[122] Article 37.1 of the Model Grant Agreement: *Before disclosing results of activities raising security issues to a third party (including affiliated entities), a beneficiary must inform the coordinator — which must request written approval from the Commission/Agency.* Article 37.2: *Activities related to 'classified deliverables' must comply with the 'security requirements' until they are declassified. Action tasks related to classified deliverables may not be subcontracted without prior explicit written approval from the Commission/Agency. The beneficiaries must inform the coordinator — which must immediately inform the Commission/Agency — of any changes in the security context and — if necessary —request for Annex 1 to be amended (see Article 55).*

Appendix: Copy of Medical University Berlin ethical approval number EA2/133/14

CHARITÉ

Charité | 10117 Berlin

Herrn
PD Dr. med. Christoph Knosalla
DHZB
Augustenburger Platz 1
13353 Berlin

Ethikkommission
Ethikausschuss 2 am Campus Virchow-Klinikum
Vorsitzender: Prof. Dr. jur. R. Seeland

Geschäftsführung: Dr. med. Katja Orzechowski
ethikkommission@charite.de

Korrespondenzadresse: Charitéplatz 1, 10117 Berlin
Tel.: 030/450-517222
Fax: 030/450-517952

http://ethikkommission.charite.de

Datum: 05.03.2015

Systemmedizin der Herzinsuffizienz (SMART) – Simulierung eines Herzklappenersatzes und dessen Auswirkung auf den Herzmuskel
Antragsnummer: EA2/133/14
Vorgang vom 17.02.2015, Eingang am 19.02.2015

hiermit bestätigen wir Ihnen den Eingang des Schreibens von Frau Hübler vom 17.02.2015 mit folgenden Anlagen:

- Ethikantrag, Version vom 13.02.2015
- Patienteninformation, Version vom 29.01.2015
- Einwilligungserklärung, Version vom 29.01.2015

Die Auflagen laut Votum vom 11.12.2014 sind damit erfüllt. Wir wünschen viel Erfolg bei der Durchführung der o.g. Studie.

Mit freundlichen Grüßen

Prof. Dr. jur. R. Seeland
Vorsitzender

ESTIMATED BUDGET FOR THE ACTION (page 1 of 2)

	Estimated eligible[1] costs (per budget category)									EU contribution			Additional information		
	A. Direct personnel costs				B. Direct costs of subcontracting	[C. Direct costs of fin. support]	D. Other direct costs	E. Indirect costs[2]	Total costs	Reimbursement rate %	Maximum EU contribution[3]	Maximum grant amount[4]	Information for indirect costs	Information for auditors	Other information:
	A.1 Employees (or equivalent) A.2 Natural persons under direct contract A.3 Seconded persons [A.6 Personnel for providing access to research infrastructure]		A.4 SME owners without salary A.5 Beneficiaries that are natural persons without salary				D.1 Travel D.2 Equipment D.3 Other goods and services D.4 Costs of large research infrastructure						Estimated costs of in-kind contributions not used on premises	Declaration of costs under Point D.4	Estimated costs of beneficiaries/ linked third parties not receiving EU funding
Form of costs[6]	Actual	Unit[7]	Unit[8]		Actual	Actual	Actual	Flat-rate[9] 25%							
	(a)	Total (b)	No hours	Total (c)	(d)	(e)	(f)	(g)=0,25x ((a)+(b)+ (c)+(f) +[(h1)+(h2)]- (m))	(i)= (a)+(b)+(c)+ (d)+(e)+(f)+ (g)+(h1)+(h2)+(h3)	(j)	(k)	(l)	(m)	Yes/No	
1. USFD	395616.00	0.00			0.00	0.00	57615.02	113307.76	566538.78	100.00	566538.78	566538.77	0.00	No	
2. ANSYS	190000.00	0.00			0.00	0.00	12839.19	50709.80	253548.99	100.00	253548.99	253548.99	0.00	No	
3. CATH	260000.00	0.00			0.00	0.00	17558.93	69389.73	346948.66	100.00	346948.66	346948.66	0.00	No	
4. CYFRONET	249400.00	0.00			0.00	0.00	42505.12	72976.28	364881.40	100.00	364881.40	364881.40	0.00	No	
5. DHZB	302200.00	0.00			0.00	0.00	39518.28	85429.57	427147.85	100.00	427147.85	427147.85	0.00	No	
6. UR1	170964.00	0.00			0.00	0.00	22773.33	48434.33	242171.66	100.00	242171.66	242171.66	0.00	No	
7. MDC	201875.00	0.00			0.00	0.00	64000.00	66468.75	332343.75	100.00	332343.75	332343.75	0.00	No	
8. PEN	568500.00	0.00			0.00	0.00	17302.77	146450.69	732253.46	100.00	732253.46	732253.46	0.00	No	
9. PHILIPS	257000.00	0.00			0.00	0.00	13485.46	67621.37	338106.83	100.00	338106.83	338106.83	0.00	No	
10. STH	343000.00	0.00			0.00	0.00	20237.57	90809.39	454046.96	100.00	454046.96	454046.96	0.00	No	
11. THERENVA	227500.00	0.00	0.00	0.00	0.00	0.00	14691.59	60547.90	302739.49	100.00	302739.49	302739.49	0.00	No	
12. TU/e	0.00	209600.00			0.00	0.00	14758.48	56089.62	280448.10	100.00	280448.10	280448.10	0.00	No	
13. UBRIS	254540.00	0.00			0.00	0.00	30929.26	71367.32	356836.58	100.00	356836.58	356836.58	0.00	No	
Total consortium	3420595.00	209600.00		0.00	0.00	0.00	368215.00	999602.51	4998012.51		4998012.51	4998012.50	0.00		0.00

ESTIMATED BUDGET FOR THE ACTION (page 2 of 2)

(1) See Article 6 for the eligibility conditions
(2) The indirect costs covered by the operating grant (received under any EU or Euratom funding programme; see Article 6.5.(b)) are ineligible under the GA. Therefore, a beneficiary that receives an operating grant during the action's duration cannot declare indirect costs for the year(s)/reporting period(s) covered by the operating grant (see Article 6.2.E).
(3) This is the theoretical amount of EU contribution that the system calculates automatically (by multiplying all the budgeted costs by the reimbursement rate). This theoretical amount is capped by the 'maximum grant amount' (that the Commission/Agency decided to grant for the action) (see Article 5.1).
(4) The 'maximum grant amount' is the maximum grant amount decided by the Commission/Agency. It normally corresponds to the requested grant, but may be lower.
(5) Depending on its type, this specific cost category will or will not cover indirect costs. Specific unit costs that include indirect costs are: costs for energy efficiency measures in buildings, access costs for providing trans-national access to research infrastructure and costs for clinical studies.
(6) See Article 5 for the forms of costs
(7) Unit : hours worked on the action; costs per unit (hourly rate) : calculated according to beneficiary's usual accounting practice
(8) See Annex 2a 'Additional information on the estimated budget' for the details (costs per hour (hourly rate)).
(9) Flat rate : 25% of eligible direct costs, from which are excluded: direct costs of subcontracting, costs of in-kind contributions not used on premises, direct costs of financial support, and unit costs declared under budget category F if they include indirect costs
(10) See Annex 2a 'Additional information on the estimated budget' for the details (units, costs per unit).
(11) See Annex 2a 'Additional information on the estimated budget' for the details (units, costs per unit, estimated number of units, etc)
(12) Only specific unit costs that do not include indirect costs
(13) See Article 9 for beneficiaries not receiving EU funding
(14) Only for linked third parties that receive EU funding

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

ANSYS FRANCE SAS (ANSYS) SAS, 389371816, established in PLACE GEORGES POMPIDOU 14-15, MONTIGNY LE BRETONNEUX 78180 , France, FR41389371816 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘2’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

Stichting Catharina Ziekenhuis (CATH) NL6, 41087385, established in MICHELANGELOLAAN 2, EINDHOVEN 5623EJ, Netherlands, NL002655135B01 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘3’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

AKADEMIA GORNICZO-HUTNICZA IM. STANISLAWA STASZICA W KRAKOWIE (CYFRONET), 000001577, established in AL ADAMA MICKIEWICZA 30, KRAKOW 30-059, Poland, PL6750001923 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘4’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

DEUTSCHES HERZZENTRUM BERLIN (DHZB) DE2, ., established in AUGUSTENBURGER PLATZ 1, BERLIN 13353, Germany, DE136623017 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘5’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

UNIVERSITE DE RENNES I (UR1), 193509361, established in RUE DU THABOR 2, RENNES CEDEX 35065, France, FR70193509361 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘6’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

MAX-DELBRUCK-CENTRUM FUR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT (MDC), established in ROBERT ROSSLE STRASSE 10, BERLIN 13125, Germany, DE811261930 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘7’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

PHILIPS ELECTRONICS NEDERLAND B.V. (PEN) BV, 17008551, established in Boschdijk 525, EINDHOVEN 5621JG, Netherlands, NL001902106B01 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘8’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

Philips GmbH (PHILIPS) AG, HRB74560, established in Luebeckertordamm 5, Hamburg 20099, Germany, DE812927597 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘9’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST (STH), established in BEECH HILL ROAD 8, SHEFFIELD S10 2SB, United Kingdom, GB654400165 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘10’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

THERENVA (THERENVA) SAS, 500603287, established in 12 RUE PIERRE CORNEILLE, RENNES 35000, France, FR35500603287 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘11’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

TECHNISCHE UNIVERSITEIT EINDHOVEN (TU/e), 51278871, established in DEN DOLECH 2, EINDHOVEN 5612 AZ, Netherlands, NL001956218B01 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘12’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

UNIVERSITY OF BRISTOL (UBRIS) GB22, RC000648, established in TYNDALL AVENUE SENATE HOUSE, BRISTOL BS8 1TH, United Kingdom, GB991261800 ('the beneficiary'), represented for the purpose of signing this Accession Form by the undersigned,

hereby agrees

to become beneficiary No (‘13’)

in Grant Agreement No 689617 (‘the Agreement’)

between THE UNIVERSITY OF SHEFFIELD **and** *the European Union (‘the EU’), represented by the European Commission ('the Commission'),*

for the action entitled ‘Personalised Decision Support for Heart Valve Disease (EurValve)’.

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 55.

By signing this Accession Form, the beneficiary accepts the grant and agrees to implement the grant in accordance with the Agreement, with all the obligations and conditions it sets out.

SIGNATURE

For the beneficiary

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MODEL ANNEX 4 FOR H2020 GENERAL MGA — MULTI

FINANCIAL STATEMENT FOR *[BENEFICIARY [name]/ LINKED THIRD PARTY [name]]* FOR REPORTING PERIOD [reporting period]

	Eligible[1] costs (per budget category)											Receipts	EU contribution			Additional information
	A. Direct personnel costs				B. Direct costs of subcontracting	*[C. Direct costs of fin. support]*	D. Other direct costs		E. Indirect costs[2]	*[F. Costs of …]*		Total costs	Receipts	Reimbursement rate %	Maximum EU contribution[3]	Requested EU contribution	Information for indirect costs :
	A.1 Employees (or equivalent) A.2 Natural persons under direct contract A.3 Seconded persons *[A.6 Personnel for providing access to research infrastructure]*		A.4 SME owners without salary A.5 Beneficiaries that are natural persons without salary				D.1 Travel D.2 Equipment D.3 Other goods and services	*[D.4 Costs of large research infrastructure]*		*[F.1 Costs of …]*			Receipts of the action, to be reported in the last reporting period, according to Article 5.3.3				Costs of in-kind contributions not used on premises
Form of costs[4]	Actual	Unit	Unit		Actual	Actual	Actual	Actual	Flat-rate[5] 25%	Unit	Unit						
	a	Total b	No hours	Total c	d	*[e]*	f	*[g]*	h=0,25 x (a+b+ c+f+*[g]* + *[i1]*[6] +*[i2]*[6] - o)	No units	Total *[i1]*	Total *[i2]*	j = a+b+c+d+*[e]* +f +*[g]* +h+*[i1]* +*[i2]*	k	l	m	n	o
[short name beneficiary/linked third party]																	

The beneficiary/linked third party hereby confirms that:
The information provided is complete, reliable and true.
The costs declared are eligible (see Article 6).
The costs can be substantiated by adequate records and supporting documentation that will be produced upon request or in the context of checks, reviews, audits and investigations (see Articles 17, 18 and 22).
For the last reporting period: that all the receipts have been declared (see Article 5.3.3).

ⓘ Please declare all eligible costs, even if they exceed the amounts indicated in the estimated budget (see Annex 2). Only amounts that were declared in your individual financial statements can be taken into account lateron, in order to replace other costs that are found to be ineligible.

[1] See Article 6 for the eligibility conditions

[2] The indirect costs claimed must be free of any amounts covered by an operating grant (received under any EU or Euratom funding programme; see Article 6.2.E). If you have received an operating grant during this reporting period, you cannot claim any indirect costs.

[3] This is the *theoretical* amount of EU contribution that the system calculates automatically (by multiplying the reimbursement rate by the total costs declared). The amount you request (in the column 'requested EU contribution') may have to be less (e.g. if you and the other beneficiaries are above budget, if the 90% limit (see Article 21) is reached, etc).

[4] See Article 5 for the form of costs

[5] Flat rate : 25% of eligible direct costs, from which are excluded: direct costs of subcontracting, costs of in-kind contributions not used on premises, direct costs of financial support, and unit costs declared under budget category F if they include indirect costs (see Article 6.2.E)

[6] Only specific unit costs that do not include indirect costs

ANNEX 5

MODEL FOR THE CERTIFICATE ON THE FINANCIAL STATEMENTS

- **For options [*in italics in square brackets*]: choose the applicable option. Options not chosen should be deleted.**
- **For fields in [grey in square brackets]: enter the appropriate data**

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Terms of Reference for an Independent Report of Factual Findings on costs declared under a Grant Agreement financed under the Horizon 2020 Research and Innovation Framework Programme

This document sets out the '**Terms of Reference (ToR)**' under which

[OPTION 1: [insert name of the beneficiary] ('the Beneficiary')] [OPTION 2: [insert name of the linked third party] ('the Linked Third Party'), third party linked to the Beneficiary [insert name of the beneficiary] ('the Beneficiary')]

agrees to engage

[**insert legal name of the auditor**] ('the Auditor')

to produce an independent report of factual findings ('the Report') concerning the Financial Statement(s)[1] drawn up by the *[Beneficiary] [Linked Third Party]* for the Horizon 2020 grant agreement [insert number of the grant agreement, title of the action, acronym and duration from/to] ('the Agreement'), and

to issue a Certificate on the Financial Statements' ('CFS') referred to in Article 20.4 of the Agreement based on the compulsory reporting template stipulated by the Commission.

The Agreement has been concluded under the Horizon 2020 Research and Innovation Framework Programme (H2020) between the Beneficiary and *[OPTION 1: the European Union, represented by the European Commission ('the Commission')][OPTION 2: the European Atomic Energy Community (Euratom,) represented by the European Commission ('the Commission')][OPTION 3: the [Research Executive Agency (REA)] [European Research Council Executive Agency (ERCEA)] [Innovation and Networks Executive Agency (INEA)] [Executive Agency for Small and Medium-sized Enterprises (EASME)] ('the Agency'), under the powers delegated by the European Commission ('the Commission').]*

[1] By which costs under the Agreement are declared (see template 'Model Financial Statements' in Annex 4 to the Grant Agreement).

The *[Commission] [Agency]* is mentioned as a signatory of the Agreement with the Beneficiary only. The *[European Union][Euratom][Agency]* is not a party to this engagement.

1.1 Subject of the engagement

The coordinator must submit to the *[Commission][Agency]* the final report within 60 days following the end of the last reporting period which should include, amongst other documents, a CFS for each beneficiary and for each linked third party that requests a total contribution of EUR 325 000 or more, as reimbursement of actual costs and unit costs calculated on the basis of its usual cost accounting practices (see Article 20.4 of the Agreement). The CFS must cover all reporting periods of the beneficiary or linked third party indicated above.

The Beneficiary must submit to the coordinator the CFS for itself and for its linked third party(ies), if the CFS must be included in the final report according to Article 20.4 of the Agreement..

The CFS is composed of two separate documents:

- The Terms of Reference ('the ToR') to be signed by the *[Beneficiary] [Linked Third Party]* and the Auditor;
- The Auditor's Independent Report of Factual Findings ('the Report') to be issued on the Auditor's letterhead, dated, stamped and signed by the Auditor (or the competent public officer) which includes the agreed-upon procedures ('the Procedures') to be performed by the Auditor, and the standard factual findings ('the Findings') to be confirmed by the Auditor.

If the CFS must be included in the final report according to Article 20.4 of the Agreement, the request for payment of the balance relating to the Agreement cannot be made without the CFS. However, the payment for reimbursement of costs covered by the CFS does not preclude the *[Commission,][Agency,]* the European Anti-Fraud Office and the European Court of Auditors from carrying out checks, reviews, audits and investigations in accordance with Article 22 of the Agreement.

1.2 Responsibilities

The *[Beneficiary] [Linked Third Party]:*

- must draw up the Financial Statement(s) for the action financed by the Agreement in compliance with the obligations under the Agreement. The Financial Statement(s) must be drawn up according to the *[Beneficiary's] [Linked Third Party's]* accounting and book-keeping system and the underlying accounts and records;
- must send the Financial Statement(s) to the Auditor;
- is responsible and liable for the accuracy of the Financial Statement(s);
- is responsible for the completeness and accuracy of the information provided to enable the Auditor to carry out the Procedures. It must provide the Auditor with a written representation letter supporting these statements. The written representation letter must state the period covered by the statements and must be dated;
- accepts that the Auditor cannot carry out the Procedures unless it is given full access to the *[Beneficiary's] [Linked Third Party's]* staff and accounting as well as any other relevant records and documentation.

The Auditor:

- *[Option 1 by default:* is qualified to carry out statutory audits of accounting documents in accordance with Directive 2006/43/EC of the European Parliament and of the Council of 17 May 2006 on statutory audits of annual accounts and consolidated accounts, amending Council Directives 78/660/EEC and 83/349/EEC and repealing Council Directive 84/253/EEC or similar national regulations*]*.
- *[Option 2 if the Beneficiary or Linked Third Party has an independent Public Officer:* is a competent and independent Public Officer for which the relevant national authorities have established the legal capacity to audit the Beneficiary*].*
- *[Option 3 if the Beneficiary or Linked Third Party is an international organisation:* is an [internal] [external] auditor in accordance with the internal financial regulations and procedures of the international organisation*].*

The Auditor:

- must be independent from the Beneficiary *[and the Linked Third Party]*, in particular, it must not have been involved in preparing the *[Beneficiary's] [Linked Third Party's]* Financial Statement(s);
- must plan work so that the Procedures may be carried out and the Findings may be assessed;
- must adhere to the Procedures laid down and the compulsory report format;
- must carry out the engagement in accordance with this ToR;
- must document matters which are important to support the Report;
- must base its Report on the evidence gathered;
- must submit the Report to the *[Beneficiary] [Linked Third Party]*.

The Commission sets out the Procedures to be carried out by the Auditor. The Auditor is not responsible for their suitability or pertinence. As this engagement is not an assurance engagement, the Auditor does not provide an audit opinion or a statement of assurance.

1.3 Applicable Standards

The Auditor must comply with these Terms of Reference and with[2]:

- the International Standard on Related Services ('ISRS') 4400 *Engagements to perform Agreed-upon Procedures regarding Financial Information* as issued by the International Auditing and Assurance Standards Board (IAASB);
- the *Code of Ethics for Professional Accountants* issued by the International Ethics Standards Board for Accountants (IESBA). Although ISRS 4400 states that independence is not a requirement for engagements to carry out agreed-upon procedures, the *[Commission][Agency]* requires that the Auditor also complies with the Code's independence requirements.

The Auditor's Report must state that there is no conflict of interests in establishing this Report between the Auditor and the Beneficiary *[and the Linked Third Party]*, and must specify - if the service is invoiced - the total fee paid to the Auditor for providing the Report.

1.4 Reporting

The Report must be written in the language of the Agreement (see Article 20.7).

Under Article 22 of the Agreement, the [*Commission*] [*Agency*], the European Anti-Fraud Office and the Court of Auditors have the right to audit any work that is carried out under the action and for which costs are declared from [*the European Union*] [*Euratom*] budget. This includes work related to this engagement. The Auditor must provide access to all working papers (e.g. recalculation of hourly rates, verification of the time declared for the action) related to this assignment if the *[Commission] [Agency]*, the European Anti-Fraud Office or the European Court of Auditors requests them.

1.5 Timing

The Report must be provided by *[*dd Month yyyy*]*.

[2] Supreme Audit Institutions applying INTOSAI-standards may carry out the Procedures according to the corresponding International Standards of Supreme Audit Institutions and code of ethics issued by INTOSAI instead of the International Standard on Related Services ('ISRS') 4400 and the Code of Ethics for Professional Accountants issued by the IAASB and the IESBA.

1.6 Other terms

[*The [Beneficiary] [Linked Third Party] and the Auditor can use this section to agree other specific terms, such as the Auditor's fees, liability, applicable law, etc. Those specific terms must not contradict the terms specified above.*]

[legal name of the Auditor]	[legal name of the *[Beneficiary][Linked Third Party]*]
[name & function of authorised representative]	[name & function of authorised representative]
[dd Month yyyy]	[dd Month yyyy]
Signature of the Auditor	Signature of the *[Beneficiary][Linked Third Party]*

Independent Report of Factual Findings on costs declared under Horizon 2020 Research and Innovation Framework Programme

(To be printed on the Auditor's letterhead)

To

[name of contact person(s)], [Position]

[[*Beneficiary's*] [*Linked Third Party's*] name]

[Address]

[dd Month yyyy]

Dear [Name of contact person(s)],

As agreed under the terms of reference dated [dd Month yyyy]

with *[OPTION 1: [insert name of the beneficiary] ('the Beneficiary')] [OPTION 2: [insert name of the linked third party] ('the Linked Third Party'), third party linked to the Beneficiary [insert name of the beneficiary] ('the Beneficiary')],*

we

[name of the auditor] ('the Auditor'),

established at

[full address/city/state/province/country],

represented by

[name and function of an authorised representative],

have carried out the procedures agreed with you regarding the costs declared in the Financial Statement(s)[3] of the *[Beneficiary] [Linked Third Party]* concerning the grant agreement

[insert grant agreement reference: number, title of the action and acronym] ('the Agreement'),

with a total cost declared of

[total amount] EUR,

and a total of actual costs and 'direct personnel costs declared as unit costs calculated in accordance with the [*Beneficiary's*] [*Linked Third Party's*] usual cost accounting practices' declared of

[sum of total actual costs and total direct personnel costs declared as unit costs calculated in accordance with the *[Beneficiary's] [Linked Third Party's]* usual cost accounting practices] EUR

and **hereby provide our Independent Report of Factual Findings ('the Report')** using the compulsory report format agreed with you.

The Report

Our engagement was carried out in accordance with the terms of reference ('the ToR') appended to this Report. The Report includes the agreed-upon procedures ('the Procedures') carried out and the standard factual findings ('the Findings') examined.

The Procedures were carried out solely to assist the [*Commission*] [*Agency*] in evaluating whether the [*Beneficiary's*] [*Linked Third Party's*] costs in the accompanying Financial Statement(s) were declared in accordance with the Agreement. The *[Commission] [Agency]* draws its own conclusions from the Report and any additional information it may require.

[3] By which the Beneficiary declares costs under the Agreement (see template 'Model Financial Statement' in Annex 4 to the Agreement).

The scope of the Procedures was defined by the Commission. Therefore, the Auditor is not responsible for their suitability or pertinence. Since the Procedures carried out constitute neither an audit nor a review made in accordance with International Standards on Auditing or International Standards on Review Engagements, the Auditor does not give a statement of assurance on the Financial Statements.

Had the Auditor carried out additional procedures or an audit of the *[Beneficiary's] [Linked Third Party's]* Financial Statements in accordance with International Standards on Auditing or International Standards on Review Engagements, other matters might have come to its attention and would have been included in the Report.

Not applicable Findings

We examined the Financial Statement(s) stated above and considered the following Findings not applicable:

Explanation (to be removed from the Report):

*If a Finding was not applicable, it must be marked as '**N.A.**' ('Not applicable') in the corresponding row on the right-hand column of the table and means that the Finding did not have to be corroborated by the Auditor and the related Procedure(s) did not have to be carried out.*

The reasons of the non-application of a certain Finding must be obvious i.e.

i) if no cost was declared under a certain category then the related Finding(s) and Procedure(s) are not applicable;

ii) if the condition set to apply certain Procedure(s) are not met the related Finding(s) and those Procedure(s) are not applicable. For instance, for 'beneficiaries with accounts established in a currency other than euro' the Procedure and Finding related to 'beneficiaries with accounts established in euro' are not applicable. Similarly, if no additional remuneration is paid, the related Finding(s) and Procedure(s) for additional remuneration are not applicable.

List here all Findings considered not applicable for the present engagement and explain the reasons of the non-applicability.

….

Exceptions

Apart from the exceptions listed below, the *[Beneficiary] [Linked Third Party]* provided the Auditor all the documentation and accounting information needed by the Auditor to carry out the requested Procedures and evaluate the Findings.

Explanation (to be removed from the Report):

- *If the Auditor was not able to successfully complete a procedure requested, it must be marked as '**E**' ('Exception') in the corresponding row on the right-hand column of the table. The reason such as the inability to reconcile key information or the unavailability of data that prevents the Auditor from carrying out the Procedure must be indicated below.*
- *If the Auditor cannot corroborate a standard finding after having carried out the corresponding procedure, it must also be marked as '**E**' ('Exception') and, where possible, the reasons why the Finding was not fulfilled and its possible impact must be explained here below.*

List here any exceptions and add any information on the cause and possible consequences of each exception, if known. If the exception is quantifiable, include the corresponding amount.

….

Example (to be removed from the Report):

1. *The Beneficiary was unable to substantiate the Finding number 1 on … because ….*
2. *Finding number 30 was not fulfilled because the methodology used by the Beneficiary to calculate unit costs was different from the one approved by the Commission. The differences were as follows: …*
3. *After carrying out the agreed procedures to confirm the Finding number 31, the Auditor found a difference of _____ EUR. The difference can be explained by …*

Further Remarks

In addition to reporting on the results of the specific procedures carried out, the Auditor would like to make the following general remarks:

Example (to be removed from the Report):

1. *Regarding Finding number 8 the conditions for additional remuneration were considered as fulfilled because …*
2. *In order to be able to confirm the Finding number 15 we carried out the following additional procedures: ….*

Use of this Report

This Report may be used only for the purpose described in the above objective. It was prepared solely for the confidential use of the *[Beneficiary] [Linked Third Party]* and the [*Commission*] [*Agency*], and only to be submitted to the [*Commission*] [*Agency*] in connection with the requirements set out in Article 20.4 of the Agreement. The Report may not be used by the *[Beneficiary] [Linked Third Party]* or by the [*Commission*] [*Agency*] for any other purpose, nor may it

be distributed to any other parties. The [*Commission*] [*Agency*] may only disclose the Report to authorised parties, in particular to the European Anti-Fraud Office (OLAF) and the European Court of Auditors.

This Report relates only to the Financial Statement(s) submitted to the *[Commission] [Agency]* by the *[Beneficiary] [Linked Third Party]* for the Agreement. Therefore, it does not extend to any other of the [*Beneficiary's*] [*Linked Third Party's*] Financial Statement(s).

There was no conflict of interest[4] between the Auditor and the Beneficiary *[and Linked Third Party]* in establishing this Report. The total fee paid to the Auditor for providing the Report was EUR _____ (including EUR_____ of deductible VAT).

We look forward to discussing our Report with you and would be pleased to provide any further information or assistance.

[legal name of the Auditor]

[name and function of an authorised representative]

[dd Month yyyy]

Signature of the Auditor

[4] A conflict of interest arises when the Auditor's objectivity to establish the certificate is compromised in fact or in appearance when the Auditor for instance:
- was involved in the preparation of the Financial Statements;
- stands to benefit directly should the certificate be accepted;
- has a close relationship with any person representing the beneficiary;
- is a director, trustee or partner of the beneficiary; or
- is in any other situation that compromises his or her independence or ability to establish the certificate impartially.

Agreed-upon procedures to be performed and standard factual findings to be confirmed by the Auditor

The European Commission reserves the right to i) provide the auditor with additional guidance regarding the procedures to be followed or the facts to be ascertained and the way in which to present them (this may include sample coverage and findings) or to ii) change the procedures, by notifying the Beneficiary in writing. The procedures carried out by the auditor to confirm the standard factual finding are listed in the table below.

If this certificate relates to a Linked Third Party, any reference here below to 'the Beneficiary' is to be considered as a reference to 'the Linked Third Party'.

The 'result' column has three different options: 'C', 'E' and 'N.A.':

- 'C' stands for 'confirmed' and means that the auditor can confirm the 'standard factual finding' and, therefore, there is no exception to be reported.
- 'E' stands for 'exception' and means that the Auditor carried out the procedures but cannot confirm the 'standard factual finding', or that the Auditor was not able to carry out a specific procedure (e.g. because it was impossible to reconcile key information or data were unavailable),
- 'N.A.' stands for 'not applicable' and means that the Finding did not have to be examined by the Auditor and the related Procedure(s) did not have to be carried out. The reasons of the non-application of a certain Finding must be obvious i.e. i) if no cost was declared under a certain category then the related Finding(s) and Procedure(s) are not applicable; ii) if the condition set to apply certain Procedure(s) are not met then the related Finding(s) and Procedure(s) are not applicable. For instance, for 'beneficiaries with accounts established in a currency other than the euro' the Procedure related to 'beneficiaries with accounts established in euro' is not applicable. Similarly, if no additional remuneration is paid, the related Finding(s) and Procedure(s) for additional remuneration are not applicable.

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
A	**ACTUAL PERSONNEL COSTS AND UNIT COSTS CALCULATED BY THE BENEFICIARY IN ACCORDANCE WITH ITS USUAL COST ACCOUNTING PRACTICE**		

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	The Auditor draws a sample of persons whose costs were declared in the Financial Statement(s) to carry out the procedures indicated in the consecutive points of this section A. (*The sample should be selected randomly so that it is representative. Full coverage is required if there are fewer than 10 people (including employees, natural persons working under a direct contract and personnel seconded by a third party), otherwise the sample should have a minimum of 10 people, or 10% of the total, whichever number is the highest)* The Auditor sampled _____ people out of the total of _____ people.		
A.1	**PERSONNEL COSTS** <u>For the persons included in the sample and working under an employment contract or equivalent act (general procedures for individual actual personnel costs and personnel costs declared as unit costs)</u> To confirm standard factual findings 1-5 listed in the next column, the Auditor reviewed following information/documents provided by the Beneficiary: ○ a list of the persons included in the sample indicating the period(s) during which they worked for the action, their position (classification or category) and type of contract; ○ the payslips of the employees included in the sample; ○ reconciliation of the personnel costs declared in the Financial Statement(s) with the accounting system (project accounting and general ledger) and payroll system; ○ information concerning the employment status and employment conditions of personnel included in the sample, in particular their employment contracts or equivalent;	1) The employees were i) directly hired by the Beneficiary in accordance with its national legislation, ii) under the Beneficiary's sole technical supervision and responsibility and iii) remunerated in accordance with the Beneficiary's usual practices.	
		2) Personnel costs were recorded in the Beneficiary's accounts/payroll system.	
		3) Costs were adequately supported and reconciled with the accounts and payroll	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	○ the Beneficiary's usual policy regarding payroll matters (e.g. salary policy, overtime policy, variable pay); ○ applicable national law on taxes, labour and social security and ○ any other document that supports the personnel costs declared. The Auditor also verified the eligibility of all components of the retribution (see Article 6 GA) and recalculated the personnel costs for employees included in the sample.	records.	
		4) Personnel costs did not contain any ineligible elements.	
		5) There were no discrepancies between the personnel costs charged to the action and the costs recalculated by the Auditor.	
	Further procedures if 'additional remuneration' is paid To confirm standard factual findings 6-9 listed in the next column, the Auditor: ○ reviewed relevant documents provided by the Beneficiary (legal form, legal/statutory obligations, the Beneficiary's usual policy on additional remuneration, criteria used for its calculation…); ○ recalculated the amount of additional remuneration eligible for the action based on the supporting documents received (full-time or part-time work, exclusive or non-exclusive dedication to the action, etc.) to arrive at the applicable FTE/year and pro-rata rate (see data collected in the course of carrying out the procedures under A.2 'Productive hours' and A.4 'Time recording system').	6) The Beneficiary paying "additional remuneration" was a non-profit legal entity.	
		7) The amount of additional remuneration paid corresponded to the Beneficiary's usual remuneration practices and was consistently paid whenever the same kind of work or expertise was required.	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	IF ANY PART OF THE REMUNERATION PAID TO THE EMPLOYEE IS NOT MANDATORY ACCORDING TO THE NATIONAL LAW OR THE EMPLOYMENT CONTRACT ("ADDITIONAL REMUNERATION") AND IS ELIGIBLE UNDER THE PROVISIONS OF ARTICLE 6.2.A.1, THIS CAN BE CHARGED AS ELIGIBLE COST TO THE ACTION UP TO THE FOLLOWING AMOUNT: *(A) IF THE PERSON WORKS FULL TIME AND EXCLUSIVELY ON THE ACTION DURING THE FULL YEAR: UP TO EUR 8 000/YEAR;* *(B) IF THE PERSON WORKS EXCLUSIVELY ON THE ACTION BUT NOT FULL-TIME OR NOT FOR THE FULL YEAR: UP TO THE CORRESPONDING PRO-RATA AMOUNT OF EUR 8 000, OR* *(C) IF THE PERSON DOES NOT WORK EXCLUSIVELY ON THE ACTION: UP TO A PRO-RATA AMOUNT CALCULATED IN ACCORDANCE TO ARTICLE 6.2.A.1.*	8) The criteria used to calculate the additional remuneration were objective and generally applied by the Beneficiary regardless of the source of funding used.	
		9) The amount of additional remuneration included in the personnel costs charged to the action was capped at EUR 8,000 per FTE/year (up to the equivalent pro-rata amount if the person did not work on the action full-time during the year or did not work exclusively on the action).	
	Additional procedures in case "unit costs calculated by the Beneficiary in accordance with its usual cost accounting practices" is applied: Apart from carrying out the procedures indicated above to confirm standard factual findings 1-5 and, if applicable, also 6-9, the Auditor carried out following procedures to confirm standard factual findings 10-13 listed in the next column:	10) The personnel costs included in the Financial Statement were calculated in accordance with the Beneficiary's usual cost accounting practice. This methodology was consistently used in all H2020 actions.	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	○ obtained a description of the Beneficiary's usual cost accounting practice to calculate unit costs;. ○ reviewed whether the Beneficiary's usual cost accounting practice was applied for the Financial Statements subject of the present CFS; ○ verified the employees included in the sample were charged under the correct category (in accordance with the criteria used by the Beneficiary to establish personnel categories) by reviewing the contract/HR-record or analytical accounting records; ○ verified that there is no difference between the total amount of personnel costs used in calculating the cost per unit and the total amount of personnel costs recorded in the statutory accounts; ○ verified whether actual personnel costs were adjusted on the basis of budgeted or estimated elements and, if so, verified whether those elements used are actually relevant for the calculation, objective and supported by documents.	11) The employees were charged under the correct category.	
		12) Total personnel costs used in calculating the unit costs were consistent with the expenses recorded in the statutory accounts.	
		13) Any estimated or budgeted element used by the Beneficiary in its unit-cost calculation were relevant for calculating personnel costs and corresponded to objective and verifiable information.	
	<u>For natural persons included in the sample and working with the Beneficiary under a direct contract other than an employment contract, such as consultants (no subcontractors).</u> To confirm standard factual findings 14-18 listed in the next column the Auditor reviewed following information/documents provided by the Beneficiary: ○ the contracts, especially the cost, contract duration, work description, place of work, ownership of the results and reporting obligations to the Beneficiary;	14) The natural persons reported to the Beneficiary (worked under the Beneficiary's instructions).	
		15) They worked on the Beneficiary's premises (unless otherwise agreed with the Beneficiary).	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	○ the employment conditions of staff in the same category to compare costs and; ○ any other document that supports the costs declared and its registration (e.g. invoices, accounting records, etc.).	16) The results of work carried out belong to the Beneficiary.	
		17) Their costs were not significantly different from those for staff who performed similar tasks under an employment contract with the Beneficiary.	
		18) The costs were supported by audit evidence and registered in the accounts.	
	<u>For personnel seconded by a third party and included in the sample (not subcontractors)</u> To confirm standard factual findings 19-22 listed in the next column, the Auditor reviewed following information/documents provided by the Beneficiary: ○ their secondment contract(s) notably regarding costs, duration, work description, place of work and ownership of the results; ○ if there is reimbursement by the Beneficiary to the third party for the resource made available (in-kind contribution against payment): any documentation that supports the costs declared (e.g. contract, invoice, bank payment, and proof of registration in its accounting/payroll, etc.) and reconciliation of the Financial Statement(s) with the accounting system (project accounting and general ledger) as well as any proof that the amount invoiced by the third party did not include any profit;	19) Seconded personnel reported to the Beneficiary and worked on the Beneficiary's premises (unless otherwise agreed with the Beneficiary).	
		20) The results of work carried out belong to the Beneficiary.	
		If personnel is seconded against payment: 21) The costs declared were supported with documentation and recorded in the	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	○ if there is no reimbursement by the Beneficiary to the third party for the resource made available (in-kind contribution free of charge): a proof of the actual cost borne by the Third Party for the resource made available free of charge to the Beneficiary such as a statement of costs incurred by the Third Party and proof of the registration in the Third Party's accounting/payroll; ○ any other document that supports the costs declared (e.g. invoices, etc.).	Beneficiary's accounts. The third party did not include any profit.	
		If personnel is seconded free of charge: 22) The costs declared did not exceed the third party's cost as recorded in the accounts of the third party and were supported with documentation.	
A.2	**PRODUCTIVE HOURS** To confirm standard factual findings 23-28 listed in the next column, the Auditor reviewed relevant documents, especially national legislation, labour agreements and contracts and time records of the persons included in the sample, to verify that: ○ the annual productive hours applied were calculated in accordance with one of the methods described below, ○ the full-time equivalent (FTEs) ratios for employees not working full-time were correctly calculated.	23) The Beneficiary applied method [*choose one option and delete the others*] [**A**: 1720 hours] [**B**: the 'total number of hours worked'] [**C**: 'annual productive hours' used correspond to usual accounting practices]	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	If the Beneficiary applied method B, the auditor verified that the correctness in which the total number of hours worked was calculated and that the contracts specified the annual workable hours. If the Beneficiary applied method C, the auditor verified that the 'annual productive hours' applied when calculating the hourly rate were equivalent to at least 90 % of the 'standard annual workable hours'. The Auditor can only do this if the calculation of the standard annual workable hours can be supported by records, such as national legislation, labour agreements, and contracts. *BENEFICIARY'S PRODUCTIVE HOURS' FOR PERSONS WORKING FULL TIME SHALL BE ONE OF THE FOLLOWING METHODS:* ***A.*** *1720 ANNUAL PRODUCTIVE HOURS (PRO-RATA FOR PERSONS NOT WORKING FULL-TIME)* ***B.*** *THE TOTAL NUMBER OF HOURS WORKED BY THE PERSON FOR THE BENEFICIARY IN THE YEAR (THIS METHOD IS ALSO REFERRED TO AS 'TOTAL NUMBER OF HOURS WORKED' IN THE NEXT COLUMN). THE CALCULATION OF THE TOTAL NUMBER OF HOURS WORKED WAS DONE AS FOLLOWS: ANNUAL WORKABLE HOURS OF THE PERSON ACCORDING TO THE EMPLOYMENT CONTRACT, APPLICABLE LABOUR AGREEMENT OR NATIONAL LAW PLUS OVERTIME WORKED MINUS ABSENCES (SUCH AS SICK LEAVE OR SPECIAL LEAVE).*	24) Productive hours were calculated annually.	
		25) For employees not working full-time the full-time equivalent (FTE) ratio was correctly applied.	
		If the Beneficiary applied method B. 26) The calculation of the number of 'annual workable hours', overtime and absences was verifiable based on the documents provided by the Beneficiary.	
		If the Beneficiary applied method C. 27) The calculation of the number of 'standard annual workable hours' was verifiable based on the documents provided by the Beneficiary.	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	C. THE STANDARD NUMBER OF ANNUAL HOURS GENERALLY APPLIED BY THE BENEFICIARY FOR ITS PERSONNEL IN ACCORDANCE WITH ITS USUAL COST ACCOUNTING PRACTICES (THIS METHOD IS ALSO REFERRED TO AS 'TOTAL ANNUAL PRODUCTIVE HOURS' IN THE NEXT COLUMN). THIS NUMBER MUST BE AT LEAST 90% OF THE STANDARD ANNUAL WORKABLE HOURS. *'ANNUAL WORKABLE HOURS' MEANS THE PERIOD DURING WHICH THE PERSONNEL MUST BE WORKING, AT THE EMPLOYER'S DISPOSAL AND CARRYING OUT HIS/HER ACTIVITY OR DUTIES UNDER THE EMPLOYMENT CONTRACT, APPLICABLE COLLECTIVE LABOUR AGREEMENT OR NATIONAL WORKING TIME LEGISLATION.*	28) The 'annual productive hours' used for calculating the hourly rate were consistent with the usual cost accounting practices of the Beneficiary and were equivalent to at least 90 % of the 'annual workable hours'.	
A.3	**HOURLY PERSONNEL RATES** <u>I) For unit costs calculated in accordance to the Beneficiary's usual cost accounting practice (unit costs):</u> If the Beneficiary has a "Certificate on Methodology to calculate unit costs " (CoMUC) approved by the Commission, the Beneficiary provides the Auditor with a description of the approved methodology and the Commission's letter of acceptance. The Auditor verified that the Beneficiary has indeed used the methodology approved. If so, no further verification is necessary. If the Beneficiary does not have a "Certificate on Methodology" (CoMUC) approved by the	29) The Beneficiary applied [*choose one option and delete the other*]: [Option I: "Unit costs (hourly rates) were calculated in accordance with the Beneficiary's usual cost accounting practices"] [Option II: Individual hourly rates were applied]	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	Commission, or if the methodology approved was not applied, then the Auditor: o reviewed the documentation provided by the Beneficiary, including manuals and internal guidelines that explain how to calculate hourly rates; o recalculated the unit costs (hourly rates) of staff included in the sample following the results of the procedures carried out in A.1 and A.2. II) For individual hourly rates: The Auditor: o reviewed the documentation provided by the Beneficiary, including manuals and internal guidelines that explain how to calculate hourly rates; o recalculated the hourly rates of staff included in the sample following the results of the procedures carried out in A.1 and A.2. *"UNIT COSTS CALCULATED BY THE BENEFICIARY IN ACCORDANCE WITH ITS USUAL COST ACCOUNTING PRACTICES":* *IT IS CALCULATED BY DIVIDING THE TOTAL AMOUNT OF PERSONNEL COSTS OF THE CATEGORY TO WHICH THE EMPLOYEE BELONGS VERIFIED IN LINE WITH PROCEDURE A.1 BY THE NUMBER OF FTE AND THE ANNUAL TOTAL PRODUCTIVE HOURS OF THE SAME CATEGORY CALCULATED BY THE BENEFICIARY IN ACCORDANCE WITH PROCEDURE A.2.* *HOURLY RATE FOR INDIVIDUAL ACTUAL PERSONAL COSTS:* *IT IS CALCULATED BY DIVIDING THE TOTAL AMOUNT OF PERSONNEL COSTS OF AN EMPLOYEE VERIFIED IN LINE WITH*	*For option I concerning unit costs and if the Beneficiary applies the methodology approved by the Commission (CoMUC):* 30) The Beneficiary used the Commission-approved methodology to calculate hourly rates. It corresponded to the organisation's usual cost accounting practices and was applied consistently for all activities irrespective of the source of funding.	
		For option I concerning unit costs and if the Beneficiary applies a methodology not approved by the Commission: 31) The unit costs re-calculated by the Auditor were the same as the rates applied by the Beneficiary.	
		For option II concerning individual hourly rates:	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	PROCEDURE A.1 BY THE NUMBER OF ANNUAL PRODUCTIVE HOURS VERIFIED IN LINE WITH PROCEDURE A.2.	32) The individual rates re-calculated by the Auditor were the same as the rates applied by the Beneficiary.	
A.4	**TIME RECORDING SYSTEM** To verify that the time recording system ensures the fulfilment of all minimum requirements and that the hours declared for the action were correct, accurate and properly authorised and supported by documentation, the Auditor made the following checks for the persons included in the sample that declare time as worked for the action on the basis of time records: o description of the time recording system provided by the Beneficiary (registration, authorisation, processing in the HR-system); o its actual implementation; o time records were signed at least monthly by the employees (on paper or electronically) and authorised by the project manager or another manager; o the hours declared were worked within the project period; o there were no hours declared as worked for the action if HR-records showed absence due to holidays or sickness (further cross-checks with travels are carried out in B.1 below) ;	33) All persons recorded their time dedicated to the action on a **daily/ weekly/ monthly** basis using a **paper/computer-based** system. (*delete the answers that are not applicable)*	
		34) Their time-records were authorised at least monthly by the project manager or other superior.	
		35) Hours declared were worked within the project period and were consistent with the presences/absences recorded in HR-records.	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	○ the hours charged to the action matched those in the time recording system. *ONLY THE HOURS WORKED ON THE ACTION CAN BE CHARGED. ALL WORKING TIME TO BE CHARGED SHOULD BE RECORDED THROUGHOUT THE DURATION OF THE PROJECT, ADEQUATELY SUPPORTED BY EVIDENCE OF THEIR REALITY AND RELIABILITY (SEE SPECIFIC PROVISIONS BELOW FOR PERSONS WORKING EXCLUSIVELY FOR THE ACTION WITHOUT TIME RECORDS).*	36) There were no discrepancies between the number of hours charged to the action and the number of hours recorded.	
	<u>If the persons are working exclusively for the action and without time records</u> For the persons selected that worked exclusively for the action without time records, the Auditor verified evidence available demonstrating that they were in reality exclusively dedicated to the action and that the Beneficiary signed a declaration confirming that they have worked exclusively for the action.	37) The exclusive dedication is supported by a declaration signed by the Beneficiary's and by any other evidence gathered.	
B	**COSTS OF SUBCONTRACTING**		
B.1	**The Auditor obtained the detail/breakdown of subcontracting costs and sampled _____ cost items selected randomly** (*full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest*). To confirm standard factual findings 38-42 listed in the next column, the Auditor reviewed the	38) The use of claimed subcontracting costs was foreseen in Annex 1 and costs were declared in the Financial Statements under the subcontracting category.	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	following for the items included in the sample: o the use of subcontractors was foreseen in Annex 1; o subcontracting costs were declared in the subcontracting category of the Financial Statement; o supporting documents on the selection and award procedure were followed; o the Beneficiary ensured best value for money (key elements to appreciate the respect of this principle are the award of the subcontract to the bid offering best price-quality ratio, under conditions of transparency and equal treatment. In case an existing framework contract was used the Beneficiary ensured it was established on the basis of the principle of best value for money under conditions of transparency and equal treatment). In particular, i. if the Beneficiary acted as a contracting authority within the meaning of Directive 2004/18/EC or of Directive 2004/17/EC, the Auditor verified that the applicable national law on public procurement was followed and that the subcontracting complied with the Terms and Conditions of the Agreement. ii. if the Beneficiary did not fall under the above-mentioned category the Auditor verified that the Beneficiary followed their usual procurement rules and respected the Terms and Conditions of the Agreement.. For the items included in the sample the Auditor also verified that: o the subcontracts were not awarded to other Beneficiaries in the consortium;	39) There were documents of requests to different providers, different offers and assessment of the offers before selection of the provider in line with internal procedures and procurement rules. Subcontracts were awarded in accordance with the principle of best value for money. *(When different offers were not collected the Auditor explains the reasons provided by the Beneficiary under the caption "Exceptions" of the Report. The Commission will analyse this information to evaluate whether these costs might be accepted as eligible)*	
		40) The subcontracts were not awarded to other Beneficiaries of the consortium.	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	○ there were signed agreements between the Beneficiary and the subcontractor; ○ there was evidence that the services were provided by subcontractor;	41) All subcontracts were supported by signed agreements between the Beneficiary and the subcontractor.	
		42) There was evidence that the services were provided by the subcontractors.	
C	**COSTS OF PROVIDING FINANCIAL SUPPORT TO THIRD PARTIES**		
C.1	**The Auditor obtained the detail/breakdown of the costs of providing financial support to third parties and sampled _____ cost items selected randomly** (*full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest*). The Auditor verified that the following minimum conditions were met: a) the maximum amount of financial support for each third party did not exceed EUR 60 000, unless explicitly mentioned in Annex 1; b) the financial support to third parties was agreed in Annex 1 of the Agreement and the other provisions on financial support to third parties included in Annex 1 were	43) All minimum conditions were met	

Ref	Procedures	Standard factual finding	Result (C / E / N.A.)
	respected.		

D	OTHER ACTUAL DIRECT COSTS		
D.1	**COSTS OF TRAVEL AND RELATED SUBSISTENCE ALLOWANCES** **The Auditor sampled _____ cost items selected randomly** (*full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is the highest*). The Auditor inspected the sample and verified that: ○ travel and subsistence costs were consistent with the Beneficiary's usual policy for travel. In this context, the Beneficiary provided evidence of its normal policy for travel costs (e.g. use of first class tickets, reimbursement by the Beneficiary on the basis of actual costs, a lump sum or per diem) to enable the Auditor to compare the travel costs charged with this policy; ○ travel costs are correctly identified and allocated to the action (e.g. trips are directly linked to the action) by reviewing relevant supporting documents such as minutes of meetings, workshops or conferences, their registration in the correct project account, their consistency with time records or with the dates/duration of the workshop/conference; ○ no ineligible costs or excessive or reckless expenditure was declared.	44) Costs were incurred, approved and reimbursed in line with the Beneficiary's usual policy for travels.	
		45) There was a link between the trip and the action.	
		46) The supporting documents were consistent with each other regarding subject of the trip, dates, duration and reconciled with time records and accounting.	
		47) No ineligible costs or excessive or reckless expenditure was declared.	
D.2	**DEPRECIATION COSTS FOR EQUIPMENT, INFRASTRUCTURE OR OTHER ASSETS** **The Auditor sampled _____ cost items selected randomly** (*full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is the highest*). For "equipment, infrastructure or other assets" [from now on called "asset(s)"] selected in the	48) Procurement rules, principles and guides were followed.	
		49) There was a link between the grant agreement and the asset charged to the action.	

	sample the Auditor verified that: ○ the assets were acquired in conformity with the Beneficiary's internal guidelines and procedures; ○ they were correctly allocated to the action (with supporting documents such as delivery note invoice or any other proof demonstrating the link to the action) ○ they were entered in the accounting system; ○ the extent to which the assets were used for the action (as a percentage) was supported by reliable documentation (e.g. usage overview table); The Auditor recalculated the depreciation costs and verified that they were in line with the applicable rules in the Beneficiary's country and with the Beneficiary's usual accounting policy (e.g. depreciation calculated on the acquisition value). The Auditor verified that no ineligible costs such as deductible VAT, exchange rate losses, excessive or reckless expenditure were declared (see Article 6.5 GA).	50) The asset charged to the action was traceable to the accounting records and the underlying documents. 51) The depreciation method used to charge the asset to the action was in line with the applicable rules of the Beneficiary's country and the Beneficiary's usual accounting policy. 52) The amount charged corresponded to the actual usage for the action. 53) No ineligible costs or excessive or reckless expenditure were declared.	
D.3	**COSTS OF OTHER GOODS AND SERVICES** **The Auditor sampled _____ cost items selected randomly** (*full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest*). For the purchase of goods, works or services included in the sample the Auditor verified that: ○ the contracts did not cover tasks described in Annex 1;	54) Contracts for works or services did not cover tasks described in Annex 1. 55) Costs were allocated to the correct action and the goods were not placed in the inventory of durable equipment.	

	○ they were correctly identified, allocated to the proper action, entered in the accounting system (traceable to underlying documents such as purchase orders, invoices and accounting); ○ the goods were not placed in the inventory of durable equipment; ○ the costs charged to the action were accounted in line with the Beneficiary's usual accounting practices; ○ no ineligible costs or excessive or reckless expenditure were declared (see Article 6 GA). In addition, the Auditor verified that these goods and services were acquired in conformity with the Beneficiary's internal guidelines and procedures, in particular: ○ if Beneficiary acted as a contracting authority within the meaning of Directive 2004/18/EC or of Directive 2004/17/EC, the Auditor verified that the applicable national law on public procurement was followed and that the procurement contract complied with the Terms and Conditions of the Agreement. ○ if the Beneficiary did not fall into the category above, the Auditor verified that the Beneficiary followed their usual procurement rules and respected the Terms and Conditions of the Agreement. For the items included in the sample the Auditor also verified that: ○ the Beneficiary ensured best value for money (key elements to appreciate the respect of this principle are the award of the contract to the bid offering best price-quality ratio, under conditions of transparency and equal treatment. In case an existing framework contract was used the Auditor also verified that the Beneficiary ensured it was established on the basis of the principle of best value for money under conditions of transparency and equal treatment); *SUCH GOODS AND SERVICES INCLUDE, FOR INSTANCE, CONSUMABLES AND SUPPLIES, DISSEMINATION (INCLUDING OPEN ACCESS), PROTECTION OF RESULTS, SPECIFIC EVALUATION OF THE ACTION IF IT IS REQUIRED BY THE*	56) The costs were charged in line with the Beneficiary's accounting policy and were adequately supported. 57) No ineligible costs or excessive or reckless expenditure were declared. For internal invoices/charges only the cost element was charged, without any mark-ups. 58) Procurement rules, principles and guides were followed. There were documents of requests to different providers, different offers and assessment of the offers before selection of the provider in line with internal procedures and procurement rules. The purchases were made in accordance with the principle of best value for money. *(When different offers were not collected the Auditor explains the reasons provided by the Beneficiary under the*	

	AGREEMENT, CERTIFICATES ON THE FINANCIAL STATEMENTS IF THEY ARE REQUIRED BY THE AGREEMENT AND CERTIFICATES ON THE METHODOLOGY, TRANSLATIONS, REPRODUCTION.	*caption "Exceptions" of the Report. The Commission will analyse this information to evaluate whether these costs might be accepted as eligible)*	
D.4	**AGGREGATED CAPITALISED AND OPERATING COSTS OF RESEARCH INFRASTRUCTURE** The Auditor ensured the existence of a positive ex-ante assessment (issued by the EC Services) of the cost accounting methodology of the Beneficiary allowing it to apply the guidelines on direct costing for large research infrastructures in Horizon 2020. ***In the cases that a positive ex-ante assessment has been issued*** *(see the standard factual findings 59-60 on the next column)****,*** The Auditor ensured that the beneficiary has applied consistently the methodology that is explained and approved in the positive ex ante assessment; ***In the cases that a positive ex-ante assessment has NOT been issued*** *(see the standard factual findings 61 on the next column),* The Auditor verified that no costs of Large Research Infrastructure have been charged as direct costs in any costs category;	59) The costs declared as direct costs for Large Research Infrastructures (in the appropriate line of the Financial Statement) comply with the methodology described in the positive ex-ante assessment report. 60) Any difference between the methodology applied and the one positively assessed was extensively described and adjusted accordingly. 61) The direct costs declared were free from any indirect costs items related to the Large Research Infrastructure.	

	In the cases that a draft ex-ante assessment report has been issued with recommendation for further changes *(see the standard factual findings 61 on the next column),* • The Auditor followed the same procedure as above (when a positive ex-ante assessment has NOT yet been issued) and paid particular attention (testing reinforced) to the cost items for which the draft ex-ante assessment either rejected the inclusion as direct costs for Large Research Infrastructures or issued recommendations.		
E	**USE OF EXCHANGE RATES**		
E.1	a) For Beneficiaries with accounts established in a currency other than euros **The Auditor sampled _____ cost items selected randomly and verified that the exchange rates used for converting other currencies into euros were in accordance with the following rules established in the Agreement** (*full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest)*: *COSTS INCURRED IN ANOTHER CURRENCY SHALL BE CONVERTED INTO EURO AT THE AVERAGE OF THE DAILY EXCHANGE RATES PUBLISHED IN THE C SERIES OF OFFICIAL JOURNAL OF THE EUROPEAN UNION (https://www.ecb.int/stats/exchange/eurofxref/html/index.en.html), DETERMINED OVER THE CORRESPONDING REPORTING PERIOD.* *IF NO DAILY EURO EXCHANGE RATE IS PUBLISHED IN THE OFFICIAL JOURNAL OF THE EUROPEAN UNION FOR THE CURRENCY IN QUESTION, CONVERSION SHALL BE MADE AT THE AVERAGE OF THE MONTHLY ACCOUNTING RATES ESTABLISHED BY THE COMMISSION AND PUBLISHED ON ITS WEBSITE (http://ec.europa.eu/budget/contracts_grants/info_contracts/inforeuro/inforeuro_en.cfm),*	62) The exchange rates used to convert other currencies into Euros were in accordance with the rules established of the Grant Agreement and there was no difference in the final figures.	

	DETERMINED OVER THE CORRESPONDING REPORTING PERIOD.		
	b) For Beneficiaries with accounts established in euros **The Auditor sampled _____ cost items selected randomly and verified that the exchange rates used for converting other currencies into euros were in accordance with the following rules established in the Agreement** (*full coverage is required if there are fewer than 10 items, otherwise the sample should have a minimum of 10 item, or 10% of the total, whichever number is highest)*: *COSTS INCURRED IN ANOTHER CURRENCY SHALL BE CONVERTED INTO EURO BY APPLYING THE BENEFICIARY'S USUAL ACCOUNTING PRACTICES.*	63) The Beneficiary applied its usual accounting practices.	

[legal name of the audit firm]

[name and function of an authorised representative]

[dd Month yyyy]

<Signature of the Auditor>

ANNEX 6

MODEL FOR THE CERTIFICATE ON THE METHODOLOGY

- **For options [*in italics in square brackets*]: choose the applicable option. Options not chosen should be deleted.**
- **For fields in [grey in square brackets]: enter the appropriate data.**

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Terms of reference for an audit engagement for a methodology certificate in connection with one or more grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme

This document sets out the '**Terms of Reference (ToR)**' under which

[OPTION 1: [insert name of the beneficiary] ('the Beneficiary')] [OPTION 2: [insert name of the linked third party] ('the Linked Third Party'), third party linked to the Beneficiary [insert name of the beneficiary] ('the Beneficiary')]

agrees to engage

[**insert legal name of the auditor**] ('the Auditor')

to produce an independent report of factual findings ('the Report') concerning the *[Beneficiary's] [Linked Third Party's]* usual accounting practices for calculating and claiming direct personnel costs declared as unit costs ('the Methodology') in connection with grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme.

The procedures to be carried out for the assessment of the methodology will be based on the grant agreement(s) detailed below:

[title and number of the grant agreement(s)] ('the Agreement(s)')

The Agreement(s) has(have) been concluded between the Beneficiary and *[OPTION 1: the European Union, represented by the European Commission ('the Commission')][OPTION 2: the European Atomic Energy Community (Euratom,) represented by the European Commission ('the Commission')][OPTION 3: the [Research Executive Agency (REA)] [European Research Council Executive Agency (ERCEA)] [Innovation and Networks Executive Agency (INEA)] [Executive Agency for Small and Medium-sized Enterprises (EASME)] ('the Agency'), under the powers delegated by the European Commission ('the Commission').]*.

The *[Commission] [Agency]* is mentioned as a signatory of the Agreement with the Beneficiary only. The *[European Union] [Euratom] [Agency]* is not a party to this engagement.

1.1 Subject of the engagement

According to Article 18.1.2 of the Agreement, beneficiaries *[and linked third parties]* that declare direct personnel costs as unit costs calculated in accordance with their usual cost accounting practices may submit to the *[Commission] [Agency]*, for approval, a certificate on the methodology ('CoMUC') stating that there are adequate records and documentation to prove that their cost accounting practices used comply with the conditions set out in Point A of Article 6.2.

The subject of this engagement is the CoMUC which is composed of two separate documents:

- the Terms of Reference ('the ToR') to be signed by the *[Beneficiary] [Linked Third Party]* and the Auditor;

- the Auditor's Independent Report of Factual Findings ('the Report') issued on the Auditor's letterhead, dated, stamped and signed by the Auditor which includes; the standard statements ('the Statements') evaluated and signed by the *[Beneficiary] [Linked Third Party]*, the agreed-upon procedures ('the Procedures') performed by the Auditor and the standard factual findings ('the Findings') assessed by the Auditor. The Statements, Procedures and Findings are summarised in the table that forms part of the Report.

The information provided through the Statements, the Procedures and the Findings will enable the Commission to draw conclusions regarding the existence of the *[Beneficiary's] [Linked Third Party's]* usual cost accounting practice and its suitability to ensure that direct personnel costs claimed on that basis comply with the provisions of the Agreement. The Commission draws its own conclusions from the Report and any additional information it may require.

1.2 Responsibilities

The parties to this agreement are the *[Beneficiary] [Linked Third Party]* and the Auditor.

The *[Beneficiary] [Linked Third Party]:*

- is responsible for preparing financial statements for the Agreement(s) ('the Financial Statements') in compliance with those Agreements;
- is responsible for providing the Financial Statement(s) to the Auditor and enabling the Auditor to reconcile them with the *[Beneficiary's] [Linked Third Party's]* accounting and bookkeeping system and the underlying accounts and records. The Financial Statement(s) will be used as a basis for the procedures which the Auditor will carry out under this ToR;
- is responsible for its Methodology and liable for the accuracy of the Financial Statement(s);
- is responsible for endorsing or refuting the Statements indicated under the heading 'Statements to be made by the Beneficiary/ Linked Third Party' in the first column of the table that forms part of the Report;
- must provide the Auditor with a signed and dated representation letter;
- accepts that the ability of the Auditor to carry out the Procedures effectively depends upon the *[Beneficiary] [Linked Third Party]* providing full and free access to the *[Beneficiary's] [Linked Third Party's]* staff and to its accounting and other relevant records.

The Auditor:

- *[Option 1 by default: is qualified to carry out statutory audits of accounting documents in accordance with Directive 2006/43/EC of the European Parliament and of the Council of 17 May 2006 on statutory audits of annual accounts and consolidated accounts, amending Council Directives 78/660/EEC and 83/349/EEC and repealing Council Directive 84/253/EEC or similar national regulations]*.
- *[Option 2 if the Beneficiary or Linked Third Party has an independent Public Officer: is a competent and independent Public Officer for which the relevant national authorities have established the legal capacity to audit the Beneficiary]*.
- *[Option 3 if the Beneficiary or Linked Third Party is an international organisation: is an [internal] [external] auditor in accordance with the internal financial regulations and procedures of the international organisation]*.

The Auditor:

- must be independent from the Beneficiary *[and the Linked Third Party]*, in particular, it must not have been involved in preparing the Beneficiary's *[and Linked Third Party's]* Financial Statement(s);
- must plan work so that the Procedures may be carried out and the Findings may be assessed;
- must adhere to the Procedures laid down and the compulsory report format;
- must carry out the engagement in accordance with these ToR;
- must document matters which are important to support the Report;
- must base its Report on the evidence gathered;
- must submit the Report to the *[Beneficiary] [Linked Third Party]*.

The Commission sets out the Procedures to be carried out and the Findings to be endorsed by the Auditor. The Auditor is not responsible for their suitability or pertinence. As this engagement is not an assurance engagement the Auditor does not provide an audit opinion or a statement of assurance.

1.3 Applicable Standards

The Auditor must comply with these Terms of Reference and with[1]:

- the International Standard on Related Services ('ISRS') 4400 *Engagements to perform Agreed-upon Procedures regarding Financial Information* as issued by the International Auditing and Assurance Standards Board (IAASB);
- the *Code of Ethics for Professional Accountants* issued by the International Ethics Standards Board for Accountants (IESBA). Although ISRS 4400 states that independence is not a requirement for engagements to carry out agreed-upon procedures, the Commission requires that the Auditor also complies with the Code's independence requirements.

The Auditor's Report must state that there was no conflict of interests in establishing this Report between the Auditor and the Beneficiary *[and the Linked Third Party]* that could have a bearing on the Report, and must specify – if the service is invoiced - the total fee paid to the Auditor for providing the Report.

1.4 Reporting

The Report must be written in the language of the Agreement (see Article 20.7 of the Agreement).

Under Article 22 of the Agreement, the Commission, *[the Agency]*, the European Anti-Fraud Office and the Court of Auditors have the right to audit any work that is carried out under the action and for which costs are claimed from [*the European Union*] [*Euratom*] budget. This includes work related to this engagement. The Auditor must provide access to all working papers related to this assignment if the Commission*, [the Agency]*, the European Anti-Fraud Office or the European Court of Auditors requests them.

1.5 Timing

The Report must be provided by [dd Month yyyy].

[1] Supreme Audit Institutions applying INTOSAI-standards may carry out the Procedures according to the corresponding International Standards of Supreme Audit Institutions and code of ethics issued by INTOSAI instead of the International Standard on Related Services ('ISRS') 4400 and the Code of Ethics for Professional Accountants issued by the IAASB and the IESBA.

1.6 Other Terms

[The [Beneficiary] [Linked Third Party] and the Auditor can use this section to agree other specific terms, such as the Auditor's fees, liability, applicable law, etc. Those specific terms must not contradict the terms specified above.]

[legal name of the Auditor]	[legal name of the [Beneficiary] [Linked Third Party]]
[name & title of authorised representative]	[name & title of authorised representative]
[dd Month yyyy]	[dd Month yyyy]
Signature of the Auditor Signature	Signature of the *[Beneficiary] [Linked Third Party]*

Independent report of factual findings on the methodology concerning grant agreements financed under the Horizon 2020 Research and Innovation Framework Programme

(To be printed on letterhead paper of the auditor)

To

[name of contact person(s)], [Position]

[[Beneficiary's] [Linked Third Party's] name]

[Address]

[dd Month yyyy]

Dear [Name of contact person(s)],

As agreed under the terms of reference dated [dd Month yyyy]

with *[OPTION 1: [insert name of the beneficiary] ('the Beneficiary')] [OPTION 2: [insert name of the linked third party] ('the Linked Third Party'), third party linked to the Beneficiary [insert name of the beneficiary] ('the Beneficiary')]*,

we

[name of the auditor] ('the Auditor'),

established at

[full address/city/state/province/country],

represented by

[name and function of an authorised representative],

have carried out the agreed-upon procedures ('the Procedures') and provide hereby our Independent Report of Factual Findings ('the Report'), concerning the *[Beneficiary's] [Linked Third Party's]* usual accounting practices for calculating and declaring direct personnel costs declared as unit costs ('the Methodology').

You requested certain procedures to be carried out in connection with the grant(s)

[title and number of the grant agreement(s)] ('the Agreement(s)').

The Report

Our engagement was carried out in accordance with the terms of reference ('the ToR') appended to this Report. The Report includes: the standard statements ('the Statements') made by the *[Beneficiary] [Linked Third Party]*, the agreed-upon procedures ('the Procedures') carried out and the standard factual findings ('the Findings') confirmed by us.

The engagement involved carrying out the Procedures and assessing the Findings and the documentation requested appended to this Report, the results of which the Commission uses to draw conclusions regarding the acceptability of the Methodology applied by the *[Beneficiary] [Linked Third Party]*.

The Report covers the methodology used from [dd Month yyyy]. In the event that the *[Beneficiary] [Linked Third Party]* changes this methodology, the Report will not be applicable to any Financial Statement[2] submitted thereafter.

The scope of the Procedures and the definition of the standard statements and findings were determined solely by the Commission. Therefore, the Auditor is not responsible for their suitability or pertinence.

Since the Procedures carried out constitute neither an audit nor a review made in accordance with International Standards on Auditing or International Standards on Review Engagements, we do not

[2] Financial Statement in this context refers solely to Annex 4 of the Agreement by which the Beneficiary declares costs under the Agreement.

give a statement of assurance on the costs declared on the basis of the *[Beneficiary's] [Linked Third Party's]* Methodology. Had we carried out additional procedures or had we performed an audit or review in accordance with these standards, other matters might have come to its attention and would have been included in the Report.

Exceptions

Apart from the exceptions listed below, the *[Beneficiary] [Linked Third Party]* agreed with the standard Statements and provided the Auditor all the documentation and accounting information needed by the Auditor to carry out the requested Procedures and corroborate the standard Findings.

List here any exception and add any information on the cause and possible consequences of each exception, if known. If the exception is quantifiable, also indicate the corresponding amount.

…..

Explanation of possible exceptions in the form of examples (to be removed from the Report):

i. the [Beneficiary] [Linked Third Party] did not agree with the standard Statement number … because…;

ii. the Auditor could not carry out the procedure … established because …. (e.g. due to the inability to reconcile key information or the unavailability or inconsistency of data);

iii. the Auditor could not confirm or corroborate the standard Finding number … because ….

Remarks

We would like to add the following remarks relevant for the proper understanding of the Methodology applied by the [Beneficiary] [Linked Third Party] or the results reported:

Example (to be removed from the Report):

Regarding the methodology applied to calculate hourly rates …

Regarding standard Finding 15 it has to be noted that …

The [Beneficiary] [Linked Third Party] explained the deviation from the benchmark statement XXIV concerning time recording for personnel with no exclusive dedication to the action in the following manner: …

Annexes

Please provide the following documents to the auditor and annex them to the report when submitting this CoMUC to the Commission:

1. Brief description of the methodology for calculating personnel costs, productive hours and hourly rates;
2. Brief description of the time recording system in place;
3. An example of the time records used by the [*Beneficiary] [Linked Third Party*];
4. Description of any budgeted or estimated elements applied, together with an explanation as to why they are relevant for calculating the personnel costs and how they are based on objective and verifiable information;
5. A summary sheet with the hourly rate for direct personnel declared by the [*Beneficiary*] [*Linked Third Party*] and recalculated by the Auditor for each staff member included in the sample (the names do not need to be reported);
6. A comparative table summarising for each person selected in the sample a) the time claimed by the [*Beneficiary*] [*Linked Third Party*] in the Financial Statement(s) and b) the time according to the time record verified by the Auditor;
7. A copy of the letter of representation provided to the Auditor.

Use of this Report

This Report has been drawn up solely for the purpose given under Point 1.1 Reasons for the engagement.

The Report:

- is confidential and is intended to be submitted to the Commission by the [*Beneficiary*] [*Linked Third Party*] in connection with Article 18.1.2 of the Agreement;
- may not be used by the [*Beneficiary*] [*Linked Third Party*] or by the Commission for any other purpose, nor distributed to any other parties;
- may be disclosed by the Commission only to authorised parties, in particular the European Anti-Fraud Office (OLAF) and the European Court of Auditors.
- relates only to the usual cost accounting practices specified above and does not constitute a report on the Financial Statements of the [*Beneficiary*] [*Linked Third Party*].

No conflict of interest[3] exists between the Auditor and the Beneficiary *[and the Linked Third Party*] that could have a bearing on the Report. The total fee paid to the Auditor for producing the Report was EUR _____ (including EUR _____ of deductible VAT).

[3] A conflict of interest arises when the Auditor's objectivity to establish the certificate is compromised in fact or in appearance when the Auditor for instance:

- was involved in the preparation of the Financial Statements;

We look forward to discussing our Report with you and would be pleased to provide any further information or assistance which may be required.

Yours sincerely

[legal name of the Auditor]

[name and title of the authorised representative]

[dd Month yyyy]

Signature of the Auditor

- stands to benefit directly should the certificate be accepted;

- has a close relationship with any person representing the beneficiary;

- is a director, trustee or partner of the beneficiary; or

- is in any other situation that compromises his or her independence or ability to establish the certificate impartially.

Statements to be made by the Beneficiary/Linked Third Party ('the Statements') and Procedures to be carried out by the Auditor ('the Procedures') and standard factual findings ('the Findings') to be confirmed by the Auditor

The Commission reserves the right to provide the auditor with guidance regarding the Statements to be made, the Procedures to be carried out or the Findings to be ascertained and the way in which to present them. The Commission reserves the right to vary the Statements, Procedures or Findings by written notification to the Beneficiary/Linked Third Party to adapt the procedures to changes in the grant agreement(s) or to any other circumstances.

If this methodology certificate relates to the Linked Third Party's usual accounting practices for calculating and claiming direct personnel costs declared as unit costs any reference here below to 'the Beneficiary' is to be considered as a reference to 'the Linked Third Party'.

Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
A. Use of the Methodology I. The cost accounting practice described below has been in use since *[*dd Month yyyy*]*. II. The next planned alteration to the methodology used by the Beneficiary will be from [dd Month yyyy*]*.	**Procedure:** ✓ The Auditor checked these dates against the documentation the Beneficiary has provided. **Factual finding:** 1. The dates provided by the Beneficiary were consistent with the documentation.
B. Description of the Methodology III. The methodology to calculate unit costs is being used in a consistent manner and is reflected in the relevant procedures. *[Please describe the methodology your entity uses to calculate personnel costs, productive hours and hourly rates, present your description to the Auditor and annex it to this certificate]* *[If the statement of section "B. Description of the methodology" cannot be endorsed by the Beneficiary or there is no written methodology to calculate unit costs it should be listed here below and reported as exception by the Auditor in the main Report of*	**Procedure:** ✓ The Auditor reviewed the description, the relevant manuals and/or internal guidance documents describing the methodology. **Factual finding:** 2. The brief description was consistent with the relevant manuals, internal guidance and/or other documentary evidence the Auditor has reviewed. 3. The methodology was generally applied by the Beneficiary as part of its usual costs accounting practices.

Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
Factual Findings: - *…]*	
C. **Personnel costs** <u>General</u> IV. The unit costs (hourly rates) are limited to salaries including during parental leave, social security contributions, taxes and other costs included in the remuneration required under national law and the employment contract or equivalent appointing act; V. Employees are hired directly by the Beneficiary in accordance with national law, and work under its sole supervision and responsibility; VI. The Beneficiary remunerates its employees in accordance with its usual practices. This means that personnel costs are charged in line with the Beneficiary's usual payroll policy (e.g. salary policy, overtime policy, variable pay) and no special conditions exist for employees assigned to tasks relating to the European Union or Euratom, unless explicitly provided for in the grant agreement(s); VII. The Beneficiary allocates its employees to the relevant group/category/cost centre for the purpose of the unit cost calculation in line with the usual cost accounting practice; VIII. Personnel costs are based on the payroll system and accounting system. IX. Any exceptional adjustments of actual personnel costs resulted from relevant budgeted or estimated elements and were based on objective and verifiable information. *[Please describe the 'budgeted or estimated elements' and their relevance to personnel costs, and explain how they were reasonable and based on objective and verifiable information, present your explanation to the Auditor and annex it to this certificate].* X. Personnel costs claimed do not contain any of the following ineligible costs: costs related to return on capital; debt and debt service charges; provisions for future losses	**Procedure:** *The Auditor draws a sample of employees to carry out the procedures indicated in this section C and the following sections D to F.* *[The Auditor has drawn a random sample of 10 full-time equivalents made up of employees assigned to the action(s). If fewer than 10 full-time equivalents are assigned to the action(s), the Auditor has selected a sample of 10 full-time equivalents consisting of all employees assigned to the action(s), complemented by other employees irrespective of their assignments.].* For this sample: ✓ the Auditor reviewed all documents relating to personnel costs such as employment contracts, payslips, payroll policy (e.g. salary policy, overtime policy, variable pay policy), accounting and payroll records, applicable national tax , labour and social security law and any other documents corroborating the personnel costs claimed; ✓ in particular, the Auditor reviewed the employment contracts of the employees in the sample to verify that: i. they were employed directly by the Beneficiary in accordance with applicable national legislation; ii. they were working under the sole technical supervision and responsibility of the latter; iii. they were remunerated in accordance with the Beneficiary's usual practices; iv. they were allocated to the correct group/category/cost centre for the purposes of calculating the unit cost in line with the Beneficiary's usual cost accounting practices; ✓ the Auditor verified that any ineligible items or any costs claimed under other costs categories or costs covered by other types of grant or by other grants financed from the European Union budget have not been taken

Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
or debts; interest owed; doubtful debts; currency exchange losses; bank costs charged by the Beneficiary's bank for transfers from the Commission/Agency; excessive or reckless expenditure; deductible VAT or costs incurred during suspension of the implementation of the action. XI. Personnel costs were not declared under another EU or Euratom grant (including grants awarded by a Member State and financed by the EU budget and grants awarded by bodies other than the Commission/Agency for the purpose of implementing the EU budget). <u>If additional remuneration as referred to in the grant agreement(s) is paid</u> XII. The Beneficiary is a non-profit legal entity; XIII. The additional remuneration is part of the beneficiary's usual remuneration practices and paid consistently whenever the relevant work or expertise is required; XIV. The criteria used to calculate the additional remuneration are objective and generally applied regardless of the source of funding; XV. The additional remuneration included in the personnel costs used to calculate the hourly rates for the grant agreement(s) is capped at EUR 8 000 per full-time equivalent (reduced proportionately if the employee is not assigned exclusively to the action). *[If certain statement(s) of section "C. Personnel costs" cannot be endorsed by the Beneficiary they should be listed here below and reported as exception by the Auditor in the main Report of*	into account when calculating the personnel costs; ✓ the Auditor numerically reconciled the total amount of personnel costs used to calculate the unit cost with the total amount of personnel costs recorded in the statutory accounts and the payroll system. ✓ to the extent that actual personnel costs were adjusted on the basis of budgeted or estimated elements, the Auditor carefully examined those elements and checked the information source to confirm that they correspond to objective and verifiable information; ✓ if additional remuneration has been claimed, the Auditor verified that the Beneficiary was a non-profit legal entity, that the amount was capped at EUR 8 000 per full-time equivalent and that it was reduced proportionately for employees not assigned exclusively to the action(s). ✓ the Auditor recalculated the personnel costs for the employees in the sample. **Factual finding:** 4. All the components of the remuneration that have been claimed as personnel costs are supported by underlying documentation. 5. The employees in the sample were employed directly by the Beneficiary in accordance with applicable national law and were working under its sole supervision and responsibility. 6. Their employment contracts were in line with the Beneficiary's usual policy; 7. Personnel costs were duly documented and consisted solely of salaries, social security contributions (pension contributions, health insurance, unemployment fund contributions, etc.), taxes and other statutory costs included in the remuneration (holiday pay, thirteenth month's pay, etc.); 8. The totals used to calculate the personnel unit costs are consistent with those registered in the payroll and accounting records; 9. To the extent that actual personnel costs were adjusted on the basis of budgeted or estimated elements, those elements were

Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
Factual Findings: - *…]*	relevant for calculating the personnel costs and correspond to objective and verifiable information. The budgeted or estimated elements used are: — (indicate the elements and their values). 10. Personnel costs contained no ineligible elements; 11. Specific conditions for eligibility were fulfilled when additional remuneration was paid: a) the Beneficiary is registered in the grant agreements as a non-profit legal entity; b) it was paid according to objective criteria generally applied regardless of the source of funding used and c) remuneration was capped at EUR 8000 per full-time equivalent (or up to up to the equivalent pro-rata amount if the person did not work on the action full-time during the year or did not work exclusively on the action).
D. Productive hours XVI. The number of productive hours per full-time employee applied is *[delete as appropriate]*: A. 1720 productive hours per year for a person working full-time (corresponding pro-rata for persons not working full time). B. the total number of hours worked in the year by a person for the Beneficiary C. the standard number of annual hours generally applied by the beneficiary for its personnel in accordance with its usual cost accounting practices. This number must be at least 90% of the standard annual workable hours. <u>If method B is applied</u> XVII. The calculation of the total number of hours worked was done as follows: annual workable hours of the person according to the employment contract, applicable labour agreement or national law plus overtime worked minus absences (such as sick leave and special leave). XVIII. 'Annual workable hours' are hours	**Procedure (same sample basis as for Section C: Personnel costs):** ✓ The Auditor verified that the number of productive hours applied is in accordance with method A, B or C. ✓ The Auditor checked that the number of productive hours per full-time employee is correct and that it is reduced proportionately for employees not exclusively assigned to the action(s). ✓ If method B is applied the Auditor verified i) the manner in which the total number of hours worked was done and ii) that the contract specified the annual workable hours by inspecting all the relevant documents, national legislation, labour agreements and contracts. ✓ If method C is applied the Auditor reviewed the manner in which the standard number of working hours per year has been calculated by inspecting all the relevant documents, national legislation, labour agreements and contracts and verified that the number of productive hours per year used for these calculations was at least 90% of the standard number of working hours per year.

Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
during which the personnel must be working, at the employer's disposal and carrying out his/her activity or duties under the employment contract, applicable collective labour agreement or national working time legislation. XIX. The contract (applicable collective labour agreement or national working time legislation) do specify the working time enabling to calculate the annual workable hours. <u>If method C is applied</u> XX. The standard number of productive hours per year is that of a full-time equivalent; for employees not assigned exclusively to the action(s) this number is reduced proportionately. XXI. The number of productive hours per year on which the hourly rate is based i) corresponds to the Beneficiary's usual accounting practices; ii) is at least 90% of the standard number of workable (working) hours per year. XXII. Standard workable (working) hours are hours during which personnel are at the Beneficiary's disposal preforming the duties described in the relevant employment contract, collective labour agreement or national labour legislation. The number of standard annual workable (working) hours that the Beneficiary claims is supported by labour contracts, national legislation and other documentary evidence. *[If certain statement(s) of section "D. Productive hours" cannot be endorsed by the Beneficiary they should be listed here below and reported as exception by the Auditor:* - *…]*	**Factual finding:** <u>General</u> 12. The Beneficiary applied a number of productive hours consistent with method A, B or C detailed in the left-hand column. 13. The number of productive hours per year per full-time employee was accurate and was proportionately reduced for employees not working full-time or exclusively for the action. <u>If method B is applied</u> 14. The number of 'annual workable hours', overtime and absences was verifiable based on the documents provided by the Beneficiary and the calculation of the total number of hours worked was accurate. 15. The contract specified the working time enabling to calculate the annual workable hours. <u>If method C is applied</u> 16. The calculation of the number of productive hours per year corresponded to the usual costs accounting practice of the Beneficiary. 17. The calculation of the standard number of workable (working) hours per year was corroborated by the documents presented by the Beneficiary. 18. The number of productive hours per year used for the calculation of the hourly rate was at least 90% of the number of workable (working) hours per year.
E. Hourly rates The hourly rates are correct because: XXIII. Hourly rates are correctly calculated since they result from dividing annual personnel	**Procedure** ✓ The Auditor has obtained a list of all personnel rates calculated by the Beneficiary in accordance with the methodology used. ✓ The Auditor has obtained a list of all the relevant employees, based on which the

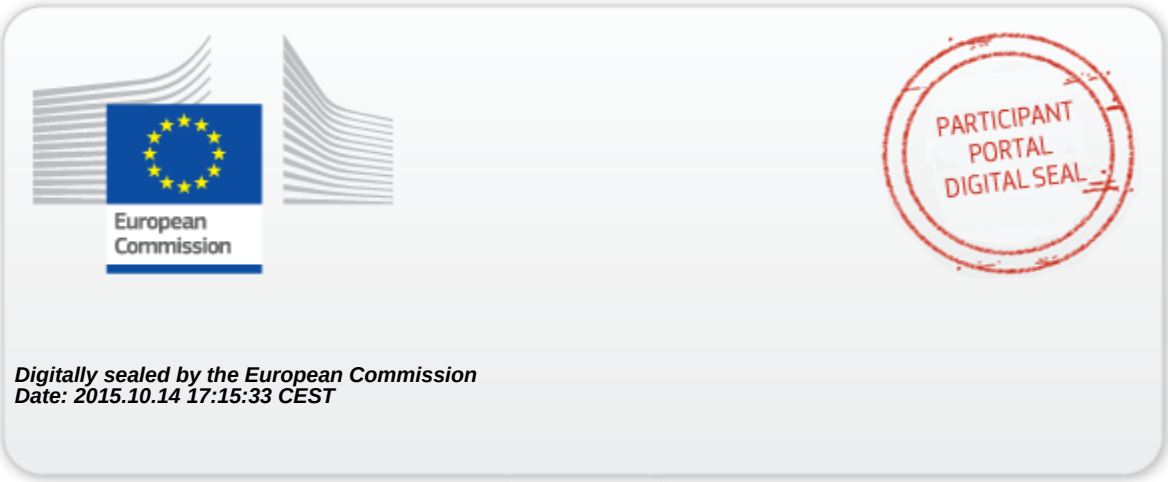
Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
costs by the productive hours of a given year and group (e.g. staff category or department or cost centre depending on the methodology applied) and they are in line with the statements made in section C. and D. above. *[If the statement of section 'E. Hourly rates' cannot be endorsed by the Beneficiary they should be listed here below and reported as exception by the Auditor:* - *…]*	personnel rate(s) are calculated. For 10 full-time equivalent employees selected at random (same sample basis as Section C: Personnel costs): ✓ The Auditor recalculated the hourly rates. ✓ The Auditor verified that the methodology applied corresponds to the usual accounting practices of the organisation and is applied consistently for all activities of the organisation on the basis of objective criteria irrespective of the source of funding. **Factual finding:** 19. No differences arose from the recalculation of the hourly rate for the employees included in the sample.
F. Time recording XXIV. Time recording is in place for all persons with no exclusive dedication to one Horizon 2020 action. At least all hours worked in connection with the grant agreement(s) are registered on a **daily/weekly/monthly** basis *[delete as appropriate]* using a **paper/computer-based system** *[delete as appropriate]*; XXV. For persons exclusively assigned to one Horizon 2020 activity the Beneficiary has either signed a declaration to that effect or has put arrangements in place to record their working time; XXVI. Records of time worked have been signed by the person concerned (on paper or electronically) and approved by the action manager or line manager at least monthly; XXVII. Measures are in place to prevent staff from: i. recording the same hours twice, ii. recording working hours during absence periods (e.g. holidays, sick leave), iii. recording more than the number of productive hours per year used to calculate the hourly rates, and	**Procedure** ✓ The Auditor reviewed the brief description, all relevant manuals and/or internal guidance describing the methodology used to record time. The Auditor reviewed the time records of the random sample of 10 full-time equivalents referred to under Section C: Personnel costs, and verified in particular: ✓ that time records were available for all persons with not exclusive assignment to the action; ✓ that time records were available for persons working exclusively for a Horizon 2020 action, or, alternatively, that a declaration signed by the Beneficiary was available for them certifying that they were working exclusively for a Horizon 2020 action; ✓ that time records were signed and approved in due time and that all minimum requirements were fulfilled; ✓ that the persons worked for the action in the periods claimed; ✓ that no more hours were claimed than the productive hours used to calculate the hourly

Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
iv. recording hours worked outside the action period. XXVIII. No working time was recorded outside the action period; XXIX. No more hours were claimed than the productive hours used to calculate the hourly personnel rates. *[Please provide a brief description of the time recording system in place together with the measures applied to ensure its reliability to the Auditor and annex it to the present certificate[4]].* *[If certain statement(s) of section "F. Time recording" cannot be endorsed by the Beneficiary they should be listed here below and reported as exception by the Auditor:* *- …]*	personnel rates; ✓ that internal controls were in place to prevent that time is recorded twice, during absences for holidays or sick leave; that more hours are claimed per person per year for Horizon 2020 actions than the number of productive hours per year used to calculate the hourly rates; that working time is recorded outside the action period; ✓ the Auditor cross-checked the information with human-resources records to verify consistency and to ensure that the internal controls have been effective. In addition, the Auditor has verified that no more hours were charged to Horizon 2020 actions per person per year than the number of productive hours per year used to calculate the hourly rates, and verified that no time worked outside the action period was charged to the action. **Factual finding:** 20. The brief description, manuals and/or internal guidance on time recording provided by the Beneficiary were consistent with management reports/records and other documents reviewed and were generally applied by the Beneficiary to produce the financial statements. 21. For the random sample time was recorded or, in the case of employees working exclusively for the action, either a signed declaration or time records were available; 22. For the random sample the time records were signed by the employee and the action manager/line manager, at least monthly. 23. Working time claimed for the action occurred in the periods claimed; 24. No more hours were claimed than the number productive hours used to calculate the hourly

[4] The description of the time recording system must state among others information on the content of the time records, its coverage (full or action time-recording, for all personnel or only for personnel involved in H2020 actions), its degree of detail (whether there is a reference to the particular tasks accomplished), its form, periodicity of the time registration and authorisation (paper or a computer-based system; on a daily, weekly or monthly basis; signed and countersigned by whom), controls applied to prevent double-charging of time or ensure consistency with HR-records such as absences and travels as well as it information flow up to its use for the preparation of the Financial Statements.

Please explain any discrepancies in the body of the Report.	
Statements to be made by Beneficiary	**Procedures to be carried out and Findings to be confirmed by the Auditor**
	personnel rates; 25. There is proof that the Beneficiary has checked that working time has not been claimed twice, that it is consistent with absence records and the number of productive hours per year, and that no working time has been claimed outside the action period. 26. Working time claimed is consistent with that on record at the human-resources department.

[official name of the** [Beneficiary] [Linked Third Party]**]	***[official name of the Auditor]***
[name and title of authorised representative]	***[name and title of authorised representative]***
[dd Month yyyy]	***[dd Month yyyy]***
<Signature of the** [Beneficiary] [Linked Third Party]**>	***<Signature** of the Auditor**>***



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