EUROPEAN COMMISSION
Research Executive Agency (REA)
Director

GRANT AGREEMENT

NUMBER — 721906 — TRACT

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

on the one part,

the **Research Executive Agency (REA)** ('the Agency'), under the power delegated by the European Commission ('the Commission'),

represented for the purposes of signature of this Agreement by Head of Unit, Research Executive Agency (REA), Excellent Science Department, Marie Sklodowska-Curie Innovative Training Networks, Klaus-Guenther BARTHEL,

and

on the other part,

1. 'the coordinator':

THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN (TCD), CHY11, established in College Green, DUBLIN 2, Ireland, IE2200007U represented for the purposes of signing the Agreement by Contracts Manager, Mary TRACEY

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

2. **OROBOROS INSTRUMENTS GmbH (OROBOROS)** GMBH, FN193145M, established in SCHOPFSTRASSE 18, INNSBRUCK 6020, Austria, ATU49093608

3. **UNIVERSITAT DE VALENCIA (UVEG)**, Decreto Nr 128/2004 , established in AVENIDA BLASCO IBANEZ 13, VALENCIA 46010, Spain, ESQ4618001D

4. **UNIVERSITA' DEGLI STUDI DI SIENA (UNISI)**, R.D. 13.10.1927 N. 2831, established in VIA BANCHI DI SOTTO 55, SIENA 53100, Italy, IT00273530527

5. **THE QUEEN'S UNIVERSITY OF BELFAST (QUB)**, XN45384, established in UNIVERSITY ROAD LANYON BUILDING, BELFAST BT7 1NN, United Kingdom, GB254799511

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 Not applicable

Annex 6 Not applicable

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 '***Training in Cancer Mechanisms and Therapeutics — TRACT***' **('action')**, as described in Annex 1.

ARTICLE 3 — DURATION AND STARTING DATE OF THE ACTION

The duration of the action will be ***48*** **months** as of *1 October 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. This does not require an amendment according to Article 55, if the action is implemented as described in Annex 1.

However, no more than 40% of the maximum grant amount (see Article 5.1) may be allocated to beneficiaries located in the same country or to any one international European interest organisation or international organisation.

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 2,877,076.80** (two million eight hundred and seventy seven thousand seventy six EURO and eighty eurocents).

5.2 Form of grant, reimbursement rate and form 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 **2,877,076.80** (two million eight hundred and seventy seven thousand seventy six EURO and eighty eurocents).

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

(a) for **costs for recruited researchers** (living, mobility and family allowances): on the basis of the amount(s) per unit set out in Annex 2 ('**unit costs**') and

(b) for **institutional costs** (research, training and networking costs and management and indirect costs): on the basis of the amount per unit set out in Annex 2 (**unit costs**).

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 Agency — when the payment of the balance is made (see Article 21.4) — in the following steps:

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

Step 2 – Limit to the maximum grant amount

Step 3 – 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 (see Article 5.2) is applied to eligible costs (unit costs; see Article 6) declared by the beneficiaries and approved by the Agency (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 improper implementation or breach of other obligations — Reduced grant amount — Calculation

If the grant is reduced (see Article 43), the Agency 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 and 2 or
- the reduced grant amount following Step 3.

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 Agency 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 Agency 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 Agency 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

Unit cost are eligible ('eligible costs') if:

(a) they are calculated as follows:

{amounts per unit set out in Annex 2

multiplied by

the number of actual units}.

(b) the number of actual units complies with the following:

- 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).

6.2 Specific conditions for costs to be eligible

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

A. Costs for recruited researchers (A.1 Living allowance, A.2 Mobility allowance and A.3 Family allowance) are eligible, if:

(a) the number of units declared:

(i) corresponds to the actual number of months spent by the recruited researchers on the research training activities and

(ii) does not exceed 36 months (per researcher)*;*

(b) the recruited researchers comply with the following conditions:

(i) be recruited by the beneficiary under an **employment contract** (or other direct contract with equivalent benefits, including social security coverage) or — if not otherwise possible under national law — under a fixed amount fellowship agreement with minimum social security coverage;

(ii) be employed for at least 3 months;

(iii) be employed full-time, unless the Agency has approved a part-time employment for personal or family reasons;

(iv) be working exclusively for the action;

(v) not have resided in the country where the research training activities take place for more than 12 months in the 3 years immediately prior to the recruitment date (and not have carried out their main activity (work, studies, etc.) in that country).

For beneficiaries that are the international European interest organisations or international organisations: not have spent with the beneficiary more than 12 months in the 3 years immediately prior to the recruitment date;

(vi) be — at the date of recruitment — an '**early stage researcher**' (i.e. in the first four years of his/her research career and not have a doctoral degree);

(c) the costs have been fully incurred for the benefit of the recruited researchers.

This latter condition is met if:

{{{**total remuneration costs** (salaries, social security contributions, taxes and other costs included in the remuneration under the employment contract or other direct contract) or **total fixed-amount fellowship costs** for the researcher during the action

plus

total mobility costs (household, relocation and travel expenses and, if they must be paid under national law, taxes, duties and social security contributions) for the researcher during the action}

plus

total family costs for the researcher during the action}

divided by

the number of actual units}.

is equal to or higher than the following amount:

{{amount per unit cost set out in Annex 2 as living allowance

plus

amount per unit cost set out in Annex 2 as mobility allowance}

plus

if it is due, amount per unit cost set out in Annex 2 as family allowance}.

The family allowance is due if the researcher has a family at the time of recruitment.

'Family' means persons linked to the researcher by marriage (or a relationship with equivalent status to a marriage recognised by the legislation of the country where this relationship was formalised) or dependent children who are actually being maintained by the researcher.

B. Institutional costs (B.1 Research, training and networking costs and B.2 Management and indirect costs) are eligible if the costs for the recruited researchers (living allowance, mobility allowance, family allowance; see above) are eligible.

6.3 Ineligible costs

'**Ineligible costs**' are:

(a) costs that do not comply with the conditions set out above (in Article 6.1), and in particular costs incurred during suspension of the action implementation (see Article 49);

(b) costs reimbursed 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 Agency for the purpose of implementing the EU or Euratom budget), in particular, management and indirect costs if the beneficiary is already receiving an operating grant financed by the EU or Euratom budget in the same period.

6.4 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

Not applicable

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

Not applicable

ARTICLE 10 — PURCHASE OF GOODS, WORKS OR SERVICES

Not applicable

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

Not applicable

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

Not applicable

ARTICLE 13 — IMPLEMENTATION OF ACTION TASKS BY SUBCONTRACTORS

Not applicable

ARTICLE 14 — IMPLEMENTATION OF ACTION TASKS BY LINKED THIRD PARTIES

Not applicable

ARTICLE 15 — FINANCIAL SUPPORT TO THIRD PARTIES

Not applicable

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

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 Agency 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 *Agency* 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 adequate records and other supporting documentation to prove the number of units declared and that the costs for recruited researchers (living allowance, mobility allowance, family allowance) have been fully incurred for the benefit of the researchers.

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 a '**progress report**' within 30 days after one year from the starting date of the action;

- organise a '**mid-term review meeting**' between the beneficiaries, the partner organisation(s) and the Agency before the deadline for the submission of the report for RP 1 (reporting period 1);

- establish a **supervisory board** of the network;

- submit any **other deliverables** identified in Annex 1, in accordance with the timing and conditions set out in it.

The beneficiaries must:

- submit a '**researcher declaration**' within 20 days after the recruitment of each researcher.

19.2 Consequences of non-compliance

If a beneficiary or the coordinator breaches any of its obligations under this Article, the Agency may apply any of the measures provided for in Chapter 6.

ARTICLE 20 — REPORTING — PAYMENT REQUESTS

20.1 Obligation to submit reports

The coordinator must submit to the *Agency* (see Article 52) the technical and financial reports set out in this Article. These reports include the requests for payments 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 24
- *RP2: from month 25 to month 48*

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 Agency;

(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 (see Article 6) for each budget category (see Annex 2).

The beneficiaries must declare all eligible costs even if 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 Agency.

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) not applicable;

(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 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**

20.5 Information on cumulative expenditure incurred

Not applicable

20.6 Currency for financial statements

Financial statements must be drafted in euro.

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 Agency 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 Agency, 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 **2,301,661.44** (two million three hundred and one thousand six hundred and sixty one EURO and forty four eurocents).

The Agency will — except if Article 48 applies — make the pre-financing payment to the coordinator within 30 days 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).

An amount of EUR **143,853.84** (one hundred and forty three thousand eight hundred and fifty three EURO and eighty four eurocents), corresponding to 5% of the maximum grant amount (see Article 5.1), is retained by the Agency 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 Agency 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 Agency 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 Agency (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 Agency 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 Agency 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 Agency,* the Commission or an*other* 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 Agency 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 Agency 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 Agency 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: BANK OF IRELAND
Address of branch: COLVILLE HOUSE: 24-26, TALBOT STREE DUBLIN 1, Ireland
Full name of the account holder: TRINITY COLLEGE DUBLIN
Full account number (including bank codes):
IBAN code: IE39BOFI90139421853025

21.9 Costs of payment transfers

The cost of the payment transfers is borne as follows:

- the Agency 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 Agency 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 Agency 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 Agency and the Commission

22.1.1 Right to carry out checks

The Agency or 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 Agency or the Commission may be assisted by external persons or bodies.

The Agency or the Commission may also request additional information in accordance with Article 17. The Agency or 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 Agency or 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.

The Agency or 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 Agency or 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 Agency or 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 Agency or 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.

The Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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[2] and No 2185/96[3] (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[4], the European Court of Auditors (ECA) may — at any moment during implementation of the action or afterwards — carry out audits.

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.

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[2] 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).

[3] 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).

[4] 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).

22.5.2 Findings in other grants

The Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency or 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 Agency 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[5].

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

The beneficiaries must ensure that researchers are aware of them.

23a.2 Consequences of non-compliance

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

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**').

[5] 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.

'**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[6] established in an EU Member State or '**associated country**'[7], if this is needed to exploit the results generated by the beneficiaries to which they are affiliated.

[6] 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.

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 researchers

The beneficiaries must — on a royalty-free basis — give access to the recruited researchers to background necessary for their research training activities under the action.

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.

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).

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.

[7] For the definition, see Article 2.1(3) Rules for Participation Regulation No 1290/2013: '**associated country**' means a non EU-country (third country) which is party to an international agreement with the Union, as identified in Article 7 of the H2020 Framework Programme Regulation No 1291/2013. Article 7 sets out the conditions for association of non-EU countries to Horizon 2020.

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 Agency ownership, to protect results

26.4.1 The Agency 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 Agency 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 Agency 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 Agency takes a positive decision, until it has taken the necessary steps to protect the results.

26.4.2 The Agency 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 Agency 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 Agency 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 Agency 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 Agency 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 Agency 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 the Marie Skłodowska-Curie grant agreement No 721906".*

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 Agency 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 the Marie Skłodowska-Curie grant agreement No 721906".*

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 Agency 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 *"Marie Skłodowska-Curie Actions"*;

- 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 Agency 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 the Marie Skłodowska-Curie grant agreement No 721906".*

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 Agency.

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 Agency responsibility

Any dissemination of results must indicate that it reflects only the author's view and that the Agency 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

(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 Agency right to object to transfers or licensing

The Agency may — up to four years after the period set out in Article 3 — object to a transfer of ownership or the exclusive licensing of results, if:

(a) it is to a third party established in a non-EU country not associated with Horizon 2020 and

(b) the Agency considers that the transfer or licence is not in line with EU interests regarding competitiveness or is inconsistent with ethical principles or security considerations.

A beneficiary that intends to transfer ownership or grant an exclusive licence must formally notify the Agency before the intended transfer or licensing takes place and:

- *identify the specific results concerned;*
- *describe in detail the new owner or licensee and the planned or potential exploitation of the results, and*
- *include a reasoned assessment of the likely impact of the transfer or licence on EU competitiveness and its consistency with ethical principles and security considerations.*

The Agency may request additional information.

If the Agency decides to object to a transfer or exclusive licence, it must formally notify the beneficiary concerned within 60 days of receiving notification (or any additional information it has requested).

No transfer or licensing may take place in the following cases:

- *pending the Agency decision, within the period set out above;*
- *if the Agency objects;*
- *until the conditions are complied with, if the Agency objection comes with conditions.*

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 researchers

The beneficiaries must — on a royalty-free basis — give access to the recruited researchers to results necessary for their research training activities under the action.

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 RECRUITED RESEARCHERS

32.1 Obligations towards recruited researchers

The beneficiaries must respect the following recruitment and working conditions for the researchers recruited under the action:

(a) 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[8] and ensure that the researchers are aware of them;

(b) advertise and publish vacancies internationally, including on the web-sites requested by the Agency;

(c) recruit the researchers, following an open, transparent, impartial and equitable recruitment procedure, on the basis of:

  (i) their scientific skills and the relevance of their research experience;

  (ii) the impact of the proposed training on the researcher's career;

  (iii) a fair gender representation (by promoting genuine equal access opportunities between men and women throughout the recruitment process);

(d) ensure that no conflict of interest exists in or arises from the recruitment;

(e) ensure that the researchers enjoy at the place of the implementation at least the same standards and working conditions as those applicable to local researchers holding a similar position;

[8] 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).

(f) ensure that the employment contract, other direct contract or fixed amount-fellowship agreement (see Article 6) specifies :

(i) the starting date and duration of the research training activities under the action;

(ii) the monthly support for the researcher under this Agreement (in euro and, if relevant, in the currency in which the remuneration is paid);

(iii) the obligation of the researcher to work exclusively for the action;

(iv) the obligation of the researcher not to receive for activities carried out in the frame of the action, other incomes than those received from the beneficiary (or any other entity referred to in Annex 1);

(v) the obligation of the researcher to inform the beneficiary as soon as possible of any events or circumstances likely to affect the Agreement (see Article 17);

(vi) the arrangements related to the intellectual property rights between the beneficiary and the researcher — during implementation of the action and afterwards;

(vii) the obligation of the researcher to maintain confidentiality (see Article 36);

(viii) the obligation of the researcher to ensure the visibility of EU funding in communications or publications and in applications for the protection of results (see Articles 27, 28, 29 and 38);

(g) assist the researchers in the administrative procedures related to their recruitment;

(h) inform the researchers about:

- the description, conditions, location and the timetable for the implementation of the research training activities under the action and the name of the supervisor;

- the rights and obligations of the beneficiary toward the researcher under this Agreement;

- the obligation of the researcher to complete and submit — at the end of the training — the evaluation questionnaire and — two years later — follow-up questionnaire provided by the Agency;

(i) ensure that the researchers do not receive, for activities carried out in the frame of the action, other incomes than those received from the beneficiaries (or any other entity referred to in Annex 1);

(j) host the researchers at their premises and provide training as well as the necessary means for implementing the action;

(k) ensure that the researchers are adequately supervised;

(l) ensure that a career development plan is established and support its implementation;

(m) ensure an appropriate exposure to the non-academic sector;

(n) limit secondments to a maximum of 30% of the actual months spent implementing the research training activities under the action.

32.2 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 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 Agency may apply any of the measures described in Chapter 6.

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[9] — 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;

[9] 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

(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 Agency 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.

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 Agency (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 Agency 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 Agency 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 Agency 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 to partner organisations 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 Agency 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[10], 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.

[10] 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).

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.

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 mainstream media coverage the beneficiaries must inform the Agency (see Article 52).

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

Unless the Agency 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 the Marie Skłodowska-Curie grant agreement No 721906".*
>
> 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 the Marie Skłodowska-Curie grant agreement No 721906".*

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 Agency.

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 Agency responsibility

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

38.2 Communication activities by the Agency

38.2.1 Right to use beneficiaries' materials, documents or information

The Agency 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 Agency's use of these materials, documents or information would risk compromising legitimate interests, the beneficiary concerned may request the Agency 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 Agency 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[11], without the right to reproduce or exploit;

(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 Agency.

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 Agency will insert the following information:

> "© – [year] – [name of the copyright owner]. All rights reserved. Licensed to the Research Executive Agency (REA) 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.

[11] 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.

ARTICLE 39 — PROCESSING OF PERSONAL DATA

39.1 Processing of personal data by the Agency and the Commission

Any personal data under the Agreement will be processed by the Agency or the Commission under Regulation No 45/2001[12] and according to the 'notifications of the processing operations' to the Data Protection Officer (DPO) of the Agency or the Commission (publicly accessible in the DPO register).

Such data will be processed by the '**data controller**' of the Agency or 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 Agency and the Commission websites.

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

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 Agency or the Commission. For this purpose, they must provide them with the service specific privacy statement (SSPS) (see above), before transmitting their data to the Agency or the Commission.

39.3 Consequences of non-compliance

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

ARTICLE 40 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE AGENCY

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

If the Agency 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 Agency.

[12] 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).

CHAPTER 5 DIVISION OF BENEFICIARIES' ROLES AND RESPONSIBILITIES — RELATIONSHIP WITH COMPLEMENTARY BENEFICIARIES — RELATIONSHIP WITH PARTNERS OF A JOINT ACTION

ARTICLE 41 — DIVISION OF BENEFICIARIES' ROLES AND RESPONSIBILITIES — RELATIONSHIP WITH COMPLEMENTARY BENEFICIARIES — RELATIONSHIP WITH PARTNERS OF A JOINT ACTION

41.1 Roles and responsibilities towards the Agency

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 Agency 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 Agency or the Commission under the Agreement, unless the Agreement requires the beneficiary to submit this information directly to the Agency or 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 Agency (in particular, providing the Agency with the information described in Article 17), unless the Agreement specifies otherwise;

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

(iv) submit the deliverables and reports to the Agency (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 Agency of the amounts paid to each beneficiary, when required under the Agreement (see Articles 44 and 50) or requested by the Agency.

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 Agency 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 Agency 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 Agency of its disagreement and the reasons why.

If the Agency 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 Agency 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 Agency — **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 Agency 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 Agency 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 Agency 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 Agency 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 Agency 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 Agency 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 Agency 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 Agency will recover the difference (see Article 44).

ARTICLE 44 — RECOVERY OF UNDUE AMOUNTS

44.1 Amount to be recovered — Calculation — Procedure

The Agency 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 Agency 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 Agency or 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 Agency, the Commission or another executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the Agency 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 Agency or 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[13] 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 Agency 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.

[13] 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).

If no observations are submitted or the Agency 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 Agency by the date in the debit note and has not submitted the report on the distribution of payments: the Agency or the Commission will **recover** the amount set out in the debit note from the coordinator (see below).

If the coordinator does not repay the Agency by the date in the debit note, but has submitted the report on the distribution of payments: the Agency 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 Agency 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)},

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 Agency will **recover** the amount:

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

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

(b) by **drawing on the Guarantee Fund**. The Agency or 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 Agency or 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 Agency.

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 Agency 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 Agency will also recover these amounts.

The Agency 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 Agency 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 Agency will **recover** the amount:

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

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

(b) by **drawing on the Guarantee Fund**. The Agency or 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 Agency or 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 Agency 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 Agency or 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 Agency.

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

45.3 Procedure

Before applying a penalty, the Agency 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 Agency 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 Agency or 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 Agency, the Commission or another executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the Agency 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 Agency or 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 Agency

The Agency 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 Agency 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 Agency 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 Agency can claim from a beneficiary will correspond to the damage caused by that beneficiary.

46.2.3 Procedure

Before claiming damages, the Agency 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 Agency 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 Agency or 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 Agency, the Commission or another executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the Agency 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 Agency or 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 Agency 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 Agency will formally notify the coordinator of the suspension and the reasons why.

The suspension will **take effect** the day notification is sent by the Agency (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 Agency 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 Agency 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 Agency 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 Agency 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 Agency 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 Agency.

If the conditions for resuming payments are met, the suspension will be **lifted**. The Agency 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 Agency 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 Agency 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 Agency.

Once circumstances allow for implementation to resume, the coordinator must immediately formally notify the Agency 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 Agency

49.2.1 Conditions

The Agency 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 Agency 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 Agency 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 Agency (see Article 46).

Suspension of the action implementation does not affect the Agency'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 Agency (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 Agency 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 Agency 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 Agency 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 Agency (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 Agency 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 Agency, (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 Agency, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The Agency 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 Agency). 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 Agency 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 Agency 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 Agency 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 Agency the amount due and the Agency 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 Agency 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 Agency the amount due. The Agency 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 Agency 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 Agency 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 Agency

50.3.1 Conditions

The Agency 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 Agency 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 Agency of the measures to ensure compliance with the obligations under the Agreement.

If the Agency 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 Agency 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 Agency 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 Agency'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 Agency (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 Agency (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 Agency, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The Agency 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 Agency). 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 Agency 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 Agency 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 Agency 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 Agency the amount due and the Agency 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 Agency 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 Agency the amount due. The Agency 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 Agency 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 Agency 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 a partner organisation), 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 Agency and 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 Agency 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 Agency** must be sent to the following address:

Research Executive Agency (REA)
Marie Sklodowska-Curie Innovative Training Networks
COV2
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[14], 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.

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;

[14] 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).

- for a change of coordinator without its agreement: the opinion of the coordinator (or proof that this opinion has been requested in writing).

The Agency 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 Agency 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 Agency'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. Actions against enforceable decisions must be brought against the Commission (not against the Agency).

ARTICLE 58 — ENTRY INTO FORCE OF THE AGREEMENT

The Agreement will enter into force on the day of signature by the Agency or the coordinator, depending on which is later.

SIGNATURES

For the coordinator

For the Agency

EUROPEAN COMMISSION
Research Executive Agency (REA)
Marie Sklodowska-Curie Innovative Training Networks

ANNEX 1 (part A)

European Training Networks

NUMBER — 721906 — TRACT

Table of Contents

1.1. The project summary

Project Number [1]	721906	Project Acronym [2]	TRACT

One form per project

General information	
Project title [3]	Training in Cancer Mechanisms and Therapeutics
Starting date [4]	01/10/2016
Duration in months [5]	48
Call (part) identifier [6]	H2020-MSCA-ITN-2016
Topic	MSCA-ITN-2016 Innovative Training Networks
Fixed EC Keywords	Pharmacology, pharmacogenomics, drug discovery and design, drug therapy, Cancer and its biological basis, Metabolism, biological basis of metabolism related disorders
Free keywords	Oral cancer, metabolism, biomakers, drug discovery

Abstract [7]

The European community requires early stage researchers (ESRs) trained in next-generation technologies for improved detection and treatment of oral and oesophageal cancers. The number of oral cancers diagnosed in the EU has increased by over 75% in the last 30 years, with long-term survival rates of only 50%. This is typically due to the late diagnosis of the disease and resistance to current therapies. Through the collaborative expertise of clinicians, biochemists, immunologists, and chemists TRACT will enable ESRs to discover novel insights into the molecular and cellular basis of these cancers and generate new diagnostic tools and therapeutics that improve patient response and survival. Each Institution brings unique but complementary expertise in cancer metabolism, metabolomics, high-resolution imaging, biomarker identification, computational modelling, medicinal chemistry, target validation, drug development and translational medicine. Industrial placements in five European countries will ensure ESRs receive specialised training in the development of next-generation technologies in such areas as whole genome sequencing, CRISPR technology, drug screening, exosome isolation and analysis, cancer imaging, metabolism and metabolite analysis in addition to the unique employment experience of working in the private sector. Courses in commercialisation, project management and presentation skills will ensure ESRs will have the ability to present their results to the entire cross-section of the European community, through public engagement. TRACT will deliver a cohort of internationally mobile cancer researchers with interdisciplinary skills who will have enhanced career prospects and be in a position to have an impact on the European and global research stage by providing new technologies that can drive entrepreneurship into the European economy and improved diagnostics and treatment options for cancer patients in Europe and beyond.

1.2. List of Beneficiaries

Project Number [1]	721906	Project Acronym [2]	TRACT

List of Beneficiaries

No	Name	Short name	Country	Project entry month[8]	Project exit month
1	THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN	TCD	Ireland	1	48
2	OROBOROS INSTRUMENTS GmbH	OROBOROS	Austria	1	48
3	UNIVERSITAT DE VALENCIA	UVEG	Spain	1	48
4	UNIVERSITA' DEGLI STUDI DI SIENA	UNISI	Italy	1	48
5	THE QUEEN'S UNIVERSITY OF BELFAST	QUB	United Kingdom	1	48

1.3. Workplan Tables - Detailed implementation

1.3.1. WT1 List of work packages

WP Number [9]	WP Title	Lead beneficiary [10]	Start month [12]	End month [13]
WP1	Ethics requirements	1 - TCD	1	48
WP2	Biomarker Discovery (research/training)	3 - UVEG	6	48
WP3	Molecular Resistance Mechanisms (research/training)	4 - UNISI	6	48
WP4	Metabolic Transformation (research/ training)	2 - OROBOROS	6	48
WP5	Training	1 - TCD	1	48
WP6	Dissemination & Exploitation	5 - QUB	1	48
WP7	Project Management	1 - TCD	1	48

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	H - Requirement No. 1	WP1	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D1.2	HCT - Requirement No. 2	WP1	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D1.3	POPD - Requirement No. 3	WP1	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D1.4	A - Requirement No. 4	WP1	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D2.1	Correlation of salivary inflammatory & glycan markers with stages of OSCC	WP2	3 - UVEG	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D2.2	Correlation of salivary marker level with tumour control in radiotherapy patients	WP2	3 - UVEG	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D2.3	Identification of molecular signatures predictive of response to chemotherapy	WP2	3 - UVEG	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D2.4	Retrospective validation of resultant predictive classifiers	WP2	3 - UVEG	Report	Confidential, only for members of the consortium (including the Commission Services)	36

Deliverable Number [14]	Deliverable Title	WP number [9]	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D2.5	PhD degree to ESRs 1-3	WP2	3 - UVEG	Other	Public	48
D3.1	Expression analysis of inflammatory caspases in OAC completed	WP3	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.2	Novel apoptotic/ autophagic modulators designed	WP3	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D3.3	Hamlet derivatives tested in OAC models	WP3	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.4	Novel apoptosis/ autophagic modulators synthesised	WP3	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.5	Identification of pathways governing drug resistance in OAC	WP3	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D3.6	Modulators tested in OOC models	WP3	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D3.7	PhD degree to ESRs 4-9	WP3	4 - UNISI	Other	Public	48
D4.1	Metabolic flux pathways in normal/ OSCC cells identified	WP4	2 - OROBOROS	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D4.2	Chemotherapy sensitivities &	WP4	2 - OROBOROS	Report	Confidential, only for members of the consortium	36

Deliverable Number [14]	Deliverable Title	WP number [9]	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
	mitochondrial functions				(including the Commission Services)	
D4.3	Identification of novel metabolic targets for OSCC	WP4	2 - OROBOROS	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D4.4	PhD degree to ESRs 10-11	WP4	2 - OROBOROS	Other	Public	48
D5.1	ESR training and progress Year 2	WP5	1 - TCD	Report	Public	36
D5.2	ESR traning and progress year 1	WP5	1 - TCD	Report	Public	18
D5.3	ESR training and progress Year 3	WP5	1 - TCD	Report	Public	44
D6.1	Dissemination diary, Year 1	WP6	5 - QUB	Report	Public	18
D6.2	Dissemination diary, Year 2	WP6	5 - QUB	Report	Public	36
D6.3	Dissemination diary, Year 3	WP6	5 - QUB	Report	Public	44
D7.1	Supervisory Board of the network	WP7	1 - TCD	Other	Confidential, only for members of the consortium (including the Commission Services)	2
D7.2	Recruitment strategy	WP7	1 - TCD	Report	Public	2
D7.3	Researcher declarations	WP7	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	7
D7.4	Progress report	WP7	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	13
D7.5	Draft periodic report	WP7	1 - TCD	Report	Confidential, only for members of the consortium (including the	24

Deliverable Number [14]	Deliverable Title	WP number [9]	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
					Commission Services)	
D7.6	Mid-term review meeting	WP7	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	26
D7.7	Consortium agreement	WP7	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	2

1.3.3. WT3 Work package descriptions

Work package number [9]	WP1	**Lead beneficiary** [10]	1 - TCD
Work package title	Ethics requirements		
Start month	1	**End month**	48

Objectives

The objective is to ensure compliance with the 'ethics requirements' set out in this work package.

Description of work and role of partners

WP1 - Ethics requirements [Months: 1-48]
TCD
This work package sets out the 'ethics requirements' that the project must comply with.

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D1.1	H - Requirement No. 1	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D1.2	HCT - Requirement No. 2	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D1.3	POPD - Requirement No. 3	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D1.4	A - Requirement No. 4	1 - TCD	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6

Description of deliverables

The 'ethics requirements' that the project must comply with are included as deliverables in this work package.

D1.1 : H - Requirement No. 1 [6]

2.1. Details on the procedures and criteria that will be used to identify/recruit research participants must be provided.
2.2. Detailed information must be provided on the informed consent procedures that will be implemented for the

participation of humans. 2.3. Approved informed consent forms and information sheet must be submitted. 2.9. Copies of ethics approvals for the research with humans must be submitted.

D1.2 : HCT - Requirement No. 2 [6]

3.1. In case human cells/tissues available commercially, details on cells/tissues type and provider must be submitted. 3.2. In case human cells/tissues are obtained within the project, details on cells/tissues type and ethics approval must be provided. 3.4. In case of human cells/tissues stored in a biobank, details on cells/tissues type must be provided, as well as details on the biobank and access to it.

D1.3 : POPD - Requirement No. 3 [6]

4.1. Copies of opinion or confirmation by the competent Institutional Data Protection Officer and/or authorization or notification by the National Data Protection Authority must be submitted (which ever applies according to the Data Protection Directive (EC Directive 95/46, currently under revision, and the national law). 4.2. If the position of a Data Protection Officer is established, their opinion/confirmation that all data collection and processing will be carried according to EU and national legislation, should be submitted. 4.4. Detailed information must be provided on the procedures that will be implemented for data collection, storage, protection, retention and destruction and confirmation that they comply with national and EU legislation. 4.5. Detailed information on the informed consent procedures that will be implemented in regard to the collection, storage and protection of personal data must be submitted on request. 4.6. Templates of the informed consent forms and information sheet must be submitted.

D1.4 : A - Requirement No. 4 [6]

5.1. Copies of relevant authorisations (for breeders, suppliers, users, and facilities) for animal experiments must be submitted. 5.2. Copy of project authorisation (covering also the work with genetically-modified animals, if applicable) must be submitted. 5.3. As research protocols are not defined, general information must be kept by the beneficiary in the project files on the nature of the experiments, the procedures to ensure the welfare of the animals, and how the Principle of the Three Rs will be applied. This information must be provided. 5.4. Copies of training certificates/personal licenses of the staff involved in animal experiments must be provided.

Schedule of relevant Milestones

Milestone number [18]	**Milestone title**	**Lead beneficiary**	**Due Date (in months)**	**Means of verification**
MS1	Ethics requirements	1 - TCD	6	Ethics requirements fulfilled

Work package number [9]	WP2	Lead beneficiary [10]	3 - UVEG
Work package title	Biomarker Discovery (research/training)		
Start month	6	End month	48

Objectives

(A) To train ESRs in state of the art techniques related to biomarker discovery,
(B) To identify novel panels of biomarkers for OOC,
(C) To pursue an avenue of translational research utilising identified biomarkers as therapeutic targets,
(D) To identify potential molecules for IP protection and patenting

Description of work and role of partners

WP2 - Biomarker Discovery (research/training) [Months: 6-48]
UVEG
WP 2.1. (Lead: UVEG; Participants: TCD, NIBRT; ESR 1). Identify differences in salivary glycan profiles in different disease stages of OSCC. TCD will provide expertise in inflammatory markers analysis using flow cytometry and other immune assays. NIBRT will provide expertise in glycan analysis, ranging from isolation of salivary protein glycans through to glycan structural identification using liquid chromatography and mass spectrometry technologies.

WP 2.2. (Lead: QUB; Participants: Almac Diagnostics and TCD; ESR 2). Develop integromic biomarkers capable of predicting response to chemotherapy in early stage OAC. QUB together with Almac will analyse whole genome sequencing, methylation and microarray data aiding in biomarker discovery. TCD will functionally analyse the underlying biology of predictive classifiers.

WP 2.3. (Lead: UVEG; Participants: IME-SP; ESR 3). Develop a diagnostic test based on salivary inflammatory markers as a predictor of an OSCC patient's response to radiotherapy. IME-SP will utilise the Mesoscale discovery platform to determine the inflammatory cytokine profile of patient samples.

Participation per Partner

Partner number and short name [10]
1 - TCD
3 - UVEG
5 - QUB

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D2.1	Correlation of salivary inflammatory & glycan markers with stages of OSCC	3 - UVEG	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D2.2	Correlation of salivary marker level with tumour control	3 - UVEG	Report	Confidential, only for members of the consortium (including the	24

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
	in radiotherapy patients			Commission Services)	
D2.3	Identification of molecular signatures predictive of response to chemotherapy	3 - UVEG	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D2.4	Retrospective validation of resultant predictive classifiers	3 - UVEG	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D2.5	PhD degree to ESRs 1-3	3 - UVEG	Other	Public	48

Description of deliverables

D2.1 Report on correlation of salivary inflammatory & glycan markers with stages of OSCC (M24)
D2.2 Report on correlation of salivary marker level with tumour control in radiotherapy patients (M24)
D2.3 Report on identification of molecular signatures predictive of response to chemotherapy (M24)
D2.4 Report on retrospective validation of resultant predictive classifiers (M36)
D2.5 Awarding of PhD degree to ESRs 1-3 (M48)

D2.1 : Correlation of salivary inflammatory & glycan markers with stages of OSCC [24]

Report on correlation of salivary inflammatory & glycan markers with stages of OSCC

D2.2 : Correlation of salivary marker level with tumour control in radiotherapy patients [24]

Report on correlation of salivary marker level with tumour control in radiotherapy patients

D2.3 : Identification of molecular signatures predictive of response to chemotherapy [24]

Report on identification of molecular signatures predictive of response to chemotherapy

D2.4 : Retrospective validation of resultant predictive classifiers [36]

Report on retrospective validation of resultant predictive classifiers

D2.5 : PhD degree to ESRs 1-3 [48]

Awarding of PhD degree to ESRs 1-3

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS2	Salivary glycan assay development	3 - UVEG	24	HPLC and Mass Spectroscopy assays for salivary glycan profiles established
MS3	Whole genome sequencing, methylation	3 - UVEG	24	Generation of whole genome sequencing, methylation & microarray

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
	& microarray development			data from early stage OAC
MS4	Salivary immune based assay development	3 - UVEG	12	Immune based assay for salivary inflammatory markers established

Work package number [9]	WP3	Lead beneficiary [10]	4 - UNISI
Work package title	Molecular Resistance Mechanisms (research/training)		
Start month	6	End month	48

Objectives

Objectives
(A) To train ESRs in drug design, synthesis and testing in models of OOC;
(B) To elucidate the genetic underpinnings of drug resistance in OOC;
(C) To identify therapeutic targets and examine potential for arresting drug resistance;
(D) To identify novel agents for treating and increasing the sensitivity of OOC to cell death

Description of work and role of partners

WP3 - Molecular Resistance Mechanisms (research/training) [Months: 6-48]
UNISI
Task 3.1. (Lead: TCD; Participants: QUB, Almac Diagnostics, IME-SP; ESR 4). Analyse differentially expressed genes in responders and non-responders and identify novel drug targets for therapeutic intervention in OAC. QUB and Almac will analyse RNA-seq & microarray data to determine expression profiles in responders and non-responders. TCD will functionally analyse the biology underlying drug resistance in OAC in order to identify potential drug targets. IME-SP will provide expertise in target selection and drug development.

Task 3.2. (Lead: TCD; Participants: QUB, Opsona; ESR 5). Establish the involvement of inflammatory caspases in tumour progression and resistance in OAC. QUB will perform expression analysis of inflammatory caspases in biopsies from OAC patients. TCD and Opsona will utilise co-culture and animal models of OAC to determine the efficacy of novel Opsona and caspase inhibitors.

Task 3.3. (Lead: UNISI; Participants: TCD,Exosomics; ESR 6). Rationally design, synthesise and test novel Mcl-1 inhibitors for the treatment of OSCC. UNISI will perform computational chemistry and organic synthesis of novel Mcl-1 inhibitors that will be biologically evaluated in OSCC models in TCD. With Exosomics the miRNA markers of cell resistance contained in exosomes extracted from the media of the treated cells will be evaluated.

Task 3.4. (Lead: TCD; Participants: OROBOROS, UNISI; ESR 7). Generation of novel HAMLET derivatives for the treatment of OAC. UNISI will design and synthesise novel HAMLET derivatives which will be biologically evaluated in OAC models in OROBOROS and TCD.

Task 3.5 (Lead: UNISI; Participants: TCD,Exosomics; ESR 8). Develop highly effective novel autophagy modulators for the treatment of OSCC. UNISI will perform bioinformatics analysis, computational chemistry and organic synthesis of novel autophagy modulators that will be biologically evaluated in OSCC models in TCD. With Exosomics the miRNA markers of cell resistance contained in exosomes extracted from the media of the treated cells will be evaluated.

Task 3.6 (Lead: TCD; Participants: UVEG, Andor; ESR 9). Assess benefit of combining chemotherapeutics with autophagy inhibitors for the treatment of OSCC. UVEG will provide OSCC patient samples and will perform immunohistochemistry and PCR analysis of autophagy markers. Andor will perform live cell imaging of autophagic processes using advanced fluorescent probes. Combinations of chemotherapeutics and autophagy modulators will be assessed in OSCC cell lines

Participation per Partner

Partner number and short name [10]
1 - TCD
2 - OROBOROS
3 - UVEG
4 - UNISI

Partner number and short name [10]
5 - QUB

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D3.1	Expression analysis of inflammatory caspases in OAC completed	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.2	Novel apoptotic/ autophagic modulators designed	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D3.3	Hamlet derivatives tested in OAC models	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.4	Novel apoptosis/ autophagic modulators synthesised	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D3.5	Identification of pathways governing drug resistance in OAC	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D3.6	Modulators tested in OOC models	4 - UNISI	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D3.7	PhD degree to ESRs 4-9	4 - UNISI	Other	Public	48

Description of deliverables

3.1 Report on RNA-seq & microarray analysis of inflammatory/autophagy proteins in OAC (M24)
3.2 Report on inflammatory caspase expression profiles during OAC (M18)
3.3 Report on markers tested in OAC culture systems (M24)
3.4 Report on novel apoptotic/autophagic modulators synthesised (M24)

3.5 Report on identification of pathways governing drug resistance (M36)
3.6 Report on modulators tested in OSCC cell lines, biopsies or in vivo animal model (M36)
3.7 Awarding of PhD degree to ESRs 4-9 (M48)

D3.1 : Expression analysis of inflammatory caspases in OAC completed [24]

Report on expression analysis of inflammatory caspases in OAC

D3.2 : Novel apoptotic/autophagic modulators designed [18]

Report on novel apoptotic/autophagic modulators designed

D3.3 : Hamlet derivatives tested in OAC models [24]

Report on Hamlet derivatives tested in OAC models

D3.4 : Novel apoptosis/autophagic modulators synthesised [24]

Report on novel apoptosis/autophagic modulators synthesised

D3.5 : Identification of pathways governing drug resistance in OAC [36]

Report on identification of pathways governing drug resistance in OAC

D3.6 : Modulators tested in OOC models [36]

Report on novel apoptosis/autophagic modulators tested in models of OOC

D3.7 : PhD degree to ESRs 4-9 [48]

Awarding of PhD degree to ESRs 4-9

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS5	RNA-seq & microarray analysis of responders vs non-responders	4 - UNISI	24	Combined RNA-seq & microarray analysis of differentially expressed/ frequently mutated genes in OAC completed
MS6	Inflammatory caspases as biomarkers for OAC assessed	4 - UNISI	24	Inflammatory caspase-1, -4 and -5 expression in OAC progression/ resistance determined
MS7	Synthesis of apoptosis/autophagy modulators	4 - UNISI	24	Synthesis of Mcl-1 inhibitors and autophagy modulators completed
MS8	Screening of novel HAMLET derivatives	4 - UNISI	24	Screening of novel HAMLET derivatives in OAC models completed

Work package number [9]	WP4	Lead beneficiary [10]	2 - OROBOROS
Work package title	Metabolic Transformation (research/training)		
Start month	6	End month	48

Objectives

(A) To train ESRs in the differential metabolic profiling of cells;
(B) To identify metabolic targets that may enhance chemotherapeutic sensitivity.

Description of work and role of partners

WP4 - Metabolic Transformation (research/training) [Months: 6-48]
OROBOROS
Task 4.1 (Lead: Oroboros; Participants: TCD; ESR 10). Analyse the metabolic flux in defined stages of OSCC and correlate with chemotherapy sensitivity. TCD will measure metabolic flux through glycolysis, pentose phosphate pathway and glutaminolysis using 2H/13C NMR. Oroboros will utilise high-resolution respirometry to measure real-time bioenergetics and metabolism in normal, dysplatic and cancerous oral cells.
Task 3.2 (Lead: TCD; Participants: Oroboros; ESR 11). Correlate bioenergetics status and chemotherapy sensitivity of defined stages of OSCC to mitochondrial function. Oroboros will utilise high-resolution respirometry to measure mitochondrial respiration in normal, dysplatic and cancerous oral cells. Confocal microscopy to observe rates of mitochondrial fission, fusion and mitophagy will be performed in TCD.

Participation per Partner

Partner number and short name [10]
1 - TCD
2 - OROBOROS

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D4.1	Metabolic flux pathways in normal/OSCC cells identified	2 - OROBOROS	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D4.2	Chemotherapy sensitivities & mitochondrial functions	2 - OROBOROS	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D4.3	Identification of novel metabolic targets for OSCC	2 - OROBOROS	Report	Confidential, only for members of the consortium (including the	36

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
				Commission Services)	
D4.4	PhD degree to ESRs 10-11	2 - OROBOROS	Other	Public	48

Description of deliverables

4.1 Report on metabolic flux pathways in normal/cancer cells (M24)
4.2 Report on chemotherapy sensitivities & mitochondrial functions (M36)
4.3 Report on identification of novel metabolic targets for oral cancer cells (M36)
4.4 Awarding of PhD degree to ESRs 10-11 (M48)

D4.1 : Metabolic flux pathways in normal/OSCC cells identified [24]

Report on metabolic flux pathways in normal/OSCC cells

D4.2 : Chemotherapy sensitivities & mitochondrial functions [36]

Report on chemotherapy sensitivities & mitochondrial functions of normal, dysplastic and cancerous OSCC cells

D4.3 : Identification of novel metabolic targets for OSCC [36]

Report on the identification of novel metabolic targets for OSCC

D4.4 : PhD degree to ESRs 10-11 [48]

Awarding of PhD degree to ESRs 10-11

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS9	Development of high-resolution respirometry assay	2 - OROBOROS	12	High-resolution respirometry to assay real time bioenergetics and metabolism in oral cancer cells established
MS10	Metabolic profiling of OSCC cells	2 - OROBOROS	24	Metabolic profiles of normal, dysplastic and cancerous oral cells identified.

Work package number [9]	WP5	Lead beneficiary [10]	1 - TCD
Work package title	Training		
Start month	1	End month	48

Objectives

(A) To organise secondments, network events and travel,
(B) To monitor quality of supervision and progress of ESRs against PDPs.

Description of work and role of partners

WP5 - Training [Months: 1-48]
TCD
Task 5.1 Project Meetings (Lead: TCD; Participants: All): Project-wide meetings will be held at M6 (TCD), M18 (QUB), M30 (TCD) and M45 (UNISI), and will be an opportunity to foster multidisciplinary and intersectoral exposure. TCD will oversee organisation of the training carried out at the meetings (workshops/discussion sessions, presentations (ESRs, PIs, external keynote speakers etc.).

Task 5.2 Training Events (Lead: TCD; Participants: UNISI, UVEG, Seahorse, Oroboros, QUB, Andor, NIBRT): A number of technical and complementary skills training events are planned during the project (section 1.2.1). TCD will oversee the general organisation of these events, while the local logistics, content and delivery will be the responsibility of the event organisers. In order to ensure the highest quality training, the agenda for each training event will be submitted to the Supervisory Board for review 4 weeks in advance of the meeting. In addition, TCD will collect ESR feedback after each event and summarise the findings for the Supervisory Board to allow continuous improvement of training events.

Task 5.3 Quality and Progress Monitoring (Lead: TCD; Participants: All): The Support Team and PDPs described in section 1.3 are central to the training of all ESRs. Together, the Support Team and ESRs will be responsible for their relevant PDPs, with PDP approval granted by the Supervisory Board. TCD will ensure that the PDPs of all ESRs are approved in a timely fashion and that progress monitoring is on-going by each Support Team. TCD will ensure that six-monthly updates for each ESR are provided to the Supervisory Board and that the Supervisory Board provides timely feedback. At M18, and M30, TCD will also collect ESR feedback on the quality of supervision for presentation to the Supervisory Board.

Participation per Partner

Partner number and short name [10]
1 - TCD
2 - OROBOROS
3 - UVEG
4 - UNISI
5 - QUB

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D5.1	ESR training and progress Year 2	1 - TCD	Report	Public	36

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D5.2	ESR traning and progress year 1	1 - TCD	Report	Public	18
D5.3	ESR training and progress Year 3	1 - TCD	Report	Public	44

Description of deliverables

5.1 Report on ESR Training and Progress, Year 1 (M18)
5.2 Report on ESR Training and Progress, Year 2 (M36)
5.3 Report on ESR Training and Progress, Year 3 (M44)

D5.1 : ESR training and progress Year 2 [36]

Report on ESR training and progress Year 2

D5.2 : ESR traning and progress year 1 [18]

Report on ESR training and progress, Year 1

D5.3 : ESR training and progress Year 3 [44]

Report on ESR training and progress Year 3

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS11	PDPs completed & approved	1 - TCD	8	PDPs approved by SB

Work package number [9]	WP6	Lead beneficiary [10]	5 - QUB
Work package title	Dissemination & Exploitation		
Start month	1	End month	48

Objectives

A) To effectively communicate and disseminate the project findings to key stakeholders, including the general public, patient groups, cancer researchers, pharmaceutical/diagnostics companies,
(B) To involve ESRs in dissemination and exploitation activities associated with a European research project,
(C) To effectively manage intellectual property generated during the project.

Description of work and role of partners

WP6 - Dissemination & Exploitation [Months: 1-48]
QUB
Task 6.1 Online Dissemination (Lead: QUB; Participants: All): A project website and social media accounts will be launched at M1, and regularly updated throughout the project with content contributed by all partners. ESRs will be expected to participate actively in online dissemination activities.

Task 6.2 Media (Lead: QUB; Participants: All): A press release will be issued by TCD at M1, and will form the basis for local press releases by all partners. PIs will interact with their local Press Offices to promote the project through their existing media networks. Additional press releases will be issued to promote project findings and outward facing events over the course of the project.

Task 6.3 Dissemination and Exploitation Events (Lead: QUB; Participants: All): A number of outward-facing events are planned during the project (section 2.3), including outreach events for students and OOC patients, Researcher Nights, Open Day and Exploitation Workshop. Responsibility for the planned events will rest with the local organisers and involved ESRs, with QUB providing overall oversight and support.

Task 6.4 Publications/presentations (Lead: QUB; Participants: All): Publication of results in peer-reviewed journals and presentation at academic conferences are envisaged. A publication policy will be agreed at the start of the project, and will include processes for authorship decisions and intellectual property protection.

Task 6.5 IP Management (Lead: QUB; Participants: All): QUB will work with all partners to ensure adherence to the IP management processes established in the Consortium Agreement and Description of Work.

Participation per Partner

Partner number and short name [10]
1 - TCD
2 - OROBOROS
3 - UVEG
4 - UNISI
5 - QUB

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D6.1	Dissemination diary, Year 1	5 - QUB	Report	Public	18

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D6.2	Dissemination diary, Year 2	5 - QUB	Report	Public	36
D6.3	Dissemination diary, Year 3	5 - QUB	Report	Public	44

Description of deliverables

6.1 Online dissemination (M2)
6.2 Dissemination diary (publications, events, etc.), year 1 (M18)
6.3 Dissemination diary (publications, events, etc.), year 2 (M36)
6.4 Dissemination diary (publications, events, etc.), year 3 (M44)

D6.1 : Dissemination diary, Year 1 [18]

Dissemination diary (publications, events etc.), year 1

D6.2 : Dissemination diary, Year 2 [36]

Dissemination diary (publications, events etc), Year 2

D6.3 : Dissemination diary, Year 3 [44]

Dissemination diary (publications, events etc.), Year 3

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS12	Website, social media live	5 - QUB	1	Online assests established
MS13	Review of dissemination/ exploitation	5 - QUB	24	Interim internal assessment

Work package number [9]	WP7	Lead beneficiary [10]	1 - TCD
Work package title	Project Management		
Start month	1	End month	48

Objectives

A) To ensure effective collaboration across the project and effectively manage project risks,
B) To support recruitment processes across all sites,
C) To ensure on time submission of high quality contractual deliverables,

Description of work and role of partners

WP7 - Project Management [Months: 1-48]
TCD
Task 7.1 Oversight and integration (Lead: TCD; Participants: All): Integration of activities across all WPs is key to achieving intended research and training objectives, as well as project impact. The Coordinator (Prof. Zisterer), supported by the Project Manager will oversee all project activities and promote integration.

Task 7.2 Communications (Lead: TCD; Participants: All): TCD will establish clear internal communication mechanisms, which are essential for ensuring effective collaboration. The Project Manager (TCD) will establish a project contact list and project calendar. A process for document sharing will also be established and maintained.

Task 7.3 Risk Management (Lead: TCD; Participants: All): Implementation risks have already been identified (Table 3.2a) and will be monitored on an on-going basis by the Coordinator and Project Manager. PIs will be responsible for identifying new risks should they arise, as well as proposing mitigation measures.

Task 7.4 Recruitment (Lead TCD; Participants: All): Recruitment will be carried out through a joint, pooled strategy (D6.1) building up a previously developed successful ITN model implemented by TCD and augmented by other partner requirements. Further detail is given in section 3.2.3.

Task 7.5 Reporting (Lead: TCD; Participants: All): Deliverables and formal reports (scientific and financial) will be delivered to the Commission, as required by the Grant Agreement. TCD will be responsible for ensuring that accurate, high-quality reports are delivered on time by all beneficiaries.

Participation per Partner

Partner number and short name [10]
1 - TCD
2 - OROBOROS
3 - UVEG
4 - UNISI
5 - QUB

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
D7.1	Supervisory Board of the network	1 - TCD	Other	Confidential, only for members of the consortium (including the	2

List of deliverables

Deliverable Number [14]	Deliverable Title	Lead beneficiary	Type [15]	Dissemination level [16]	Due Date (in months) [17]
				Commission Services)	
D7.2	Recruitment strategy	1 - TCD	Report	Public	2
D7.3	Researcher declarations	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	7
D7.4	Progress report	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	13
D7.5	Draft periodic report	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D7.6	Mid-term review meeting	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	26
D7.7	Consortium agreement	1 - TCD	Report	Confidential, only for members of the consortium (including the Commission Services)	2

Description of deliverables

D7.1 : Supervisory Board of the network [2]
Supervisory board of the netwrok established

D7.2 : Recruitment strategy [2]
Recruitment strategy including recruitment of project manager

D7.3 : Researcher declarations [7]
Researcher declarations

D7.4 : Progress report [13]
Progress report

D7.5 : Draft periodic report [24]
Draft periodic report (for the purpose of the meeting)

D7.6 : Mid-term review meeting [26]
Mid-term review meeting
D7.7 : Consortium agreement [2]
Consortium agreement

Schedule of relevant Milestones

Milestone number [18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS14	Planned recruitment completed	1 - TCD	12	11 ESRs and Project Manager recruited
MS15	Internal communications	1 - TCD	6	Internal communications established
MS16	Risk management	1 - TCD	12	Risk assessments completed
MS17	Progress report	1 - TCD	13	Progress report complete
MS18	Mid term review with PO	1 - TCD	26	Review complete
MS19	End of project report	1 - TCD	48	Report submitted, all training events complete

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	Ethics requirements	WP1	1 - TCD	6	Ethics requirements fulfilled
MS2	Salivary glycan assay development	WP2	3 - UVEG	24	HPLC and Mass Spectroscopy assays for salivary glycan profiles established
MS3	Whole genome sequencing, methylation & microarray development	WP2	3 - UVEG	24	Generation of whole genome sequencing, methylation & microarray data from early stage OAC
MS4	Salivary immune based assay development	WP2	3 - UVEG	12	Immune based assay for salivary inflammatory markers established
MS5	RNA-seq & microarray analysis of responders vs non-responders	WP3	4 - UNISI	24	Combined RNA-seq & microarray analysis of differentially expressed/ frequently mutated genes in OAC completed
MS6	Inflammatory caspases as biomarkers for OAC assessed	WP3	4 - UNISI	24	Inflammatory caspase-1, -4 and -5 expression in OAC progression/resistance determined
MS7	Synthesis of apoptosis/ autophagy modulators	WP3	4 - UNISI	24	Synthesis of Mcl-1 inhibitors and autophagy modulators completed
MS8	Screening of novel HAMLET derivatives	WP3	4 - UNISI	24	Screening of novel HAMLET derivatives in OAC models completed
MS9	Development of high-resolution respirometry assay	WP4	2 - OROBOROS	12	High-resolution respirometry to assay real time bioenergetics and metabolism in oral cancer cells established
MS10	Metabolic profiling of OSCC cells	WP4	2 - OROBOROS	24	Metabolic profiles of normal, dysplastic and cancerous oral cells identified.
MS11	PDPs completed & approved	WP5	1 - TCD	8	PDPs approved by SB
MS12	Website, social media live	WP6	5 - QUB	1	Online assests established
MS13	Review of dissemination/ exploitation	WP6	5 - QUB	24	Interim internal assessment

Milestone number [18]	Milestone title	WP number [9]	Lead beneficiary	Due Date (in months) [17]	Means of verification
MS14	Planned recruitment completed	WP7	1 - TCD	12	11 ESRs and Project Manager recruited
MS15	Internal communications	WP7	1 - TCD	6	Internal communications established
MS16	Risk management	WP7	1 - TCD	12	Risk assessments completed
MS17	Progress report	WP7	1 - TCD	13	Progress report complete
MS18	Mid term review with PO	WP7	1 - TCD	26	Review complete
MS19	End of project report	WP7	1 - TCD	48	Report submitted, all training events complete

1.3.5. WT5 Critical Implementation risks and mitigation actions

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
1	ESR research projects not completed on time.	WP2, WP3, WP4	ESR projects will run for three years, while the project duration is four years, allowing a six-month buffer period in case of unforeseen delay (e.g. breakdown of equipment, illness of researcher). The ESR projects are not interdependent - delays in one project will not affect others.
2	ESRs do not achieve requisite competences	WP2, WP3, WP4, WP5	Experimental procedures and technologies are well established in the partner laboratories so this risk is minimal. Furthermore, recruited ESRs will have a demonstrated track record in experimental research. If required, affected ESRs will receive intensive training.
3	Partners do not collaborate effectively.	WP7	A dedicated Project Manager will be engaged to monitor all project activities (research and training) on a monthly basis, and flag any potential issues to the Coordinator and SB. The consortium will strive for consensus, but the Consortium Agreement will detail a clear process for conflict resolution, should the need arise. Many partners have long standing collaborations and common research goals (e.g. Zisterer group in TCD and Campiani group in UNISI have collaborated effectively for 20 years with 33 joint publications).
4	Difficulty recruiting high-quality ESRs.	WP7	Vacancies will be advertised widely and well in advance. A list of ranked reserve candidates will be held in the event that the highest ranked candidates withdraw. All PIs have a successful recruiting history with 165 PhD students supervised to completion.
5	Dispute between ESR and Support Team.	WP7	Conflict resolution mediated by the SB will be adhered to in the event of a dispute between an ESR and their Support Team. Non-academic conflicts can be dealt with by both formal and informal procedures with the Graduate Studies Office in the host institution. Academic conflicts will be highlighted to the SB.
6	ESR fails to complete PhD programme.	WP7	TRACT has extensive support mechanisms to enable ESRs to successfully meet the requirements of local PhD programmes. If an ESR wishes to leave the project early, it will be possible to award an MSc degree after 1.5 years.

1.3.6. WT6 Summary of project effort contribution

	WP1	WP2	WP3	WP4	WP5	WP6	WP7
1 - TCD		✓	✓	✓	✓	✓	✓
2 - OROBOROS			✓	✓	✓	✓	✓
3 - UVEG		✓	✓		✓	✓	✓
4 - UNISI			✓		✓	✓	✓
5 - QUB		✓	✓		✓	✓	✓

1.3.7. WT7 Tentative schedule of project reviews

No project reviews indicated

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	
ETHICS	Ethics requirement

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.

Marie Skłodowska-Curie Actions (MSCA)
Innovative Training Networks (ITN)
H2020-MSCA-ITN-2016

[TRACT–721906]

Annex 1 to the Grant Agreement
(Description of the Action)
Part B

TABLE OF CONTENTS

LIST OF PARTICIPANTS

Consortium Member	Legal Entity Short Name	Academic	Non-academic	Awards Doctoral Degrees	Country	Dept./ Division / Laboratory	Scientist-in-Charge	Role of Partner Organisation
Beneficiaries								
Trinity College Dublin	TCD	√		√	IRL	Biochemistry & Immunology /Cancer	Daniela Zisterer	
University of Valencia	UVEG	√		√	ES	Faculty of Medicine and Odontology	Jose Bagan	
University of Siena	UNISI	√		√	IT	Medicinal Chemistry	Giuseppe Campiani	
The Queen's University of Belfast	QUB	√		√	UK	Centre for Cancer Research and Cell Biology	Richard Turkington	
Oroboros Instruments	OROBOROS		√		AT	Bioenergetics	Erich Gnaiger	
Partner Organisation								
Seahorse Bioscience	Seahorse		√		UK	Metabolism & Bioenergetics	Alex Liversage	Deliver training course
National Institute for Bioprocessing Training Research	NIBRT		√		IE	Glycan Biomarkers	Pauline Rudd	Deliver training courses & host secondment
Exosomics Siena S. p. A.	Exosomics		√		IT	Exosomes	Antonio Chiesi	Host secondments
Fraunhofer Society	IME-SP		√		DE	High-Throughput Screening	Björn Windshügel	Host secondments
Andor Technology	ANDOR		√		UK	Microscopy	Orla Hanrahan	Deliver training courses & host secondments
Almac Diagnostics	ALMAC		√		UK	Bioinformatics	Timothy Davison	Host secondments
Opsona Therapeutics	OPSONA		√		IE	Cancer Immunology	Luke O'Neill	Host secondment

Data for non-academic beneficiaries:

Name	Location of research premises (city / country)	Type of R&D activities	No. of full - time employees	No. of employees in R&D	Web site	Annual turnover (approx, in Euro)	Enterprise status (Yes/No)	SME status (Yes/No)
OROBOROS	Innsbruck Austria	High-resolution respirometry	8	3.5	www.oroboros.at	3,139,000	Yes	Yes

Declarations

Name (institution / individual)	Nature of inter-relationship
Richard Kennedy (Queen's University Belfast/Almac Diagnostics)	McClay Professor in Medical Oncology, Queen's University Belfast, Vice President and Medical Director, Almac Diagnostics

1. Excellence

1.1 Quality, innovative aspects & credibility of research programme

1.1.1 Introduction

In 2012, 8.2 million people worldwide died of cancer, of which 5.3% or **over half a million deaths were accounted for by oral and oesophageal cancer (OOC)**[1]. Oral cancer includes carcinoma of the mouth (oral cavity) and the back of the mouth (oropharynx) and oesophageal cancer includes carcinoma of the oesophagus and the gastro-oesophageal junction. The predominant cause of OOC is exposure to topical carcinogens, in particular alcohol and tobacco, giving rise to squamous cell carcinomas[2] (OSCC). Adenocarcinoma, another sub-type of OOC, may also be related to smoking and alcohol abuse, but to a lesser extent than squamous cell carcinoma. Oesophageal adenocarcinomas (OAC) are mostly found to occur at the junction of the oesophagus and stomach and are associated with a history of inflammation - gastroesophageal reflux and Barrett's oesophagus (where the normal tissue lining the oesophagus changes to resemble the lining of the intestine)[3].

Despite efforts to screen for the pre-malignant condition Barrett's oesophagus and pre-operatively select OAC patients for potentially curative surgery, the **five-year survival rate in early stage disease is only 25-35%.** The incidence of OAC in men has also risen 50% in the last 25 years[4]. This is **due to late diagnosis of disease and resistance to chemotherapy**. In order to improve outcomes for OOC patients, there is an urgent need to discover biomarkers for early detection of the disease and patient monitoring/stratification, and to better understand the molecular basis of metabolic transformation and drug resistance in OOC in order to develop novel therapies.

The TRACT research training programme will carry out high-quality research in three interconnected thematic areas (Biomarker Discovery, Molecular Resistance Mechanisms and Metabolic Transformation Mechanisms) in order to **address current diagnostic, prognostic and therapeutic clinical needs in OOC**. Early stage researchers (ESRs) recruited to the project will undertake a broad-based training and research programme encompassing both basic research and clinical translation to develop methods for early diagnosis and novel treatment strategies. ESRs will particularly concentrate their research efforts on the two most common sub-types of OOC, oral squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC).

TRACT will provide ESRs with exposure to a collaborative network of European academic and industrial experts working in the complementary domains of cancer metabolism, metabolomics, high-resolution imaging, bioinformatics, biomarker identification, computational modelling, medicinal chemistry, target validation, drug development, nanotechnology and translational medicine**. Although there are many researchers working on OOC in the relevant domains listed above, there is a lack of integration between domains** - through a programme of **integrative training and research,** TRACT will bring together relevant domains to **deliver better diagnostics and therapeutics for OOC** with the overall aim of **improving patient response and survival**.

1.1.2 Research Objectives

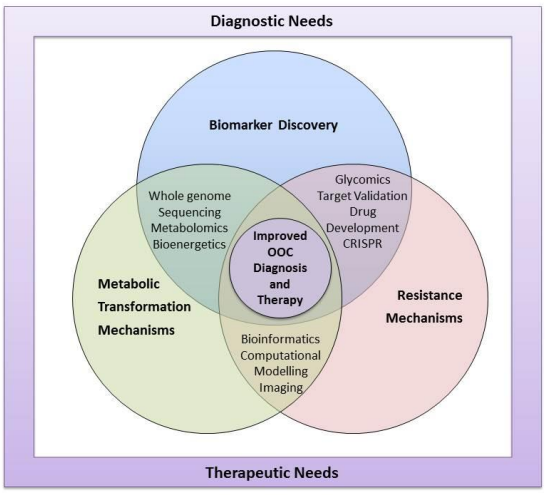
The **overall aim of the research programme** is to integrate basic and applied research in three related themes in order to deliver new diagnostic & prognostic tools and therapeutic approaches for patients with OOC.

During the project, TRACT ESRs will undertake novel research to:

1) Determine novel biomarkers at the protein, glycan and molecular level to enable early detection of OOC and to predict patient response to therapy (WP2).

2) Uncover the molecular basis of drug resistance in OOC leading to the identification of new drug targets and the development of novel cancer therapeutics (WP3).

3) Enhance knowledge of metabolic transformation in OOC leading to the identification of novel targets for therapeutic intervention (WP4).



1 http://www.wcrf.org/int/cancer-facts-figures/worldwide-data
2 Vokes EE, et al., N Engl J Med. 1993 Jan 21;328(3):184-94.
3 Lepage C1,et al., . Dig Liver Dis. 2013 Aug;45(8):625-9.
4 http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oesophagus/mortality/#source1

1.1.3 Overview of the research programme

During the project, 11 ESRs will be recruited to complete research projects in: Biomarker Discovery (WP2), Molecular Resistance Mechanisms (WP3) and Metabolic Transformation Mechanisms (WP4) (see Table 1.1a below). Outputs from WP2 will address current diagnostic clinical needs and also provide prognostic means for predicting therapeutic responses in patients, while outputs from WPs 3 and 4 will address current therapeutic unmet needs. The individual ESR projects will **integrate research across biochemistry, immunology, dental science and medicinal chemistry academic disciplines to deliver diagnostic, prognostic and therapeutic options with clinical relevance**. Through our SME/industrial partners, ESRs will be exposed to **next-generation technologies in cancer diagnosis, metabolism (including glycomics, metabolomics), genome scale CRISPR knockout and next generation sequencing, imaging, biomarker identification, exosome isolation/analysis, medicinal chemistry, target identification/validation, bioinformatics, protein structure, computational modelling and drug development.**

TRACT will implement a multi-faceted approach to discover novel diagnostic and prognostic biomarkers to enable more focused administration of current chemotherapeutics. In parallel with and complementing these studies, novel protein targets will be determined and initial PoC small molecule modulators will be discovered to serve as a starting point towards the ultimate target validation in future clinical trials. The **successful completion** of the project goals is bolstered by the fact that: (1) The ESR projects will **not be interdependent** which is a key strength of the programme; (2) each ESR will be co-supervised by an academic and industrial **world-leader** in their area of expertise thereby significantly enhancing the likelihood of success of the individual projects and of the research programme as a whole.

1.1.4 Research Methodology and approach

Table 1.1a: Work Package List

WP No	Work Package Title	Lead Beneficiary No.	Start Month	End Month	Activity Type	Lead Beneficiary Short Name	ESRs involve-ment
WP1	Research Ethics	1	6	48	Ethics	TCD	ESR1-11
WP2	Biomarker Discovery	3	6	48	Research/Training	UVEG	ESR1 -3
WP3	Resistance Mechanisms	4	6	48	Research/Training	UNISI	ESR4 - 9
WP4	Metabolic Transformation	2	6	48	Research/Training	OROBOROS	ESR10 - 11
WP5	Training	3	1	42	Training	UNISI	ESR1 - 11
WP6	Dissemination	5	1	48	Dissemination	QUB	ESR1 - 11
WP7	Project Management	1	1	48	Management	TCD	ESR on SB

Biomarker discovery (WP2)

TRACT will carry out discovery research into biomarkers associated with OOC to develop state-of-the-art diagnostic assays for 1) earlier, more reliable detection, and 2) therapeutic response prediction. Overall, research carried out under WP2 will improve OOC survival rates by developing biomarker-based assays for **earlier, more reliable disease diagnosis** and **stratification of individual patients to more effective chemotherapeutic regimes**. This comprehensive patient profiling provides essential information to the clinician, enabling earlier and more **accurate diagnosis** and the potential to administer more **appropriate treatment**. This approach will not only benefit the patient, with the potential for improved **quality of life, disease control** and **minimise side-effects** by administering more targeted treatment, but will also potentially lead to **reduced costs** for healthcare providers.

The most effective approach to reducing OOC morbidity is early detection, yet **no effective diagnostic procedures for OOC currently exist**. At present, definitive diagnosis of OOC relies upon tissue biopsy, a procedure that often yields false-negative diagnoses and results in the recovery of non-diagnostic tissue[5]. ESR 1 (UVEG recruit; NIBRT secondment) will explore the development of a biomarker-based diagnostic approach as an alternative to tissue biopsy. To date, the search for biomarkers associated with the early onset of oral squamous cell carcinoma (OSCC) has focused on a single proteomic approach and has met with only limited success[6]. ESR 1 will adopt an alternative approach using state-of-the-art multidisciplinary techniques to **determine novel salivary biomarkers at protein, glycan and molecular levels**. Saliva collection has distinct advantages over tissue and blood collection

5 Scully C, Bagan JV, et al.. Am J Dent. 2008 Aug;21(4):199-209.
6 Tung CL,et al., (2013). J Pharm Biomed Anal. J Pharm Biomed Anal. 2013 Mar 5;75:7-17.
7 Yoshizawa JM et al (2013) Clin. Microbiol. Rev. Oct;26 (4):781-791
8 Feller L et al., (2013) Oral Oncol. 2013 Sep; 49(9):887-892.

as the collection procedure is non-invasive and does not require specialised resources, and the resulting samples are safer to handle and easier to store[7]. Saliva is currently being used in many diagnostic procedures, including screening for HIV, hepatitis and ebola.[7] Currently the O'Sullivan lab in TCD has built up a biobank of saliva samples from patients exhibiting a fixed stage of oral pre-cancer/cancer along with positive pilot studies demonstrating the use of saliva as an oral cancer diagnostic tool. As inflammation has previously been linked to the pathogenesis of OSCC[8], saliva from OSCC patients will be analysed to determine the relationship between pro-inflammatory cytokine markers (TNF-α, IL-1β, IL-6, and IL-8), salivary glycan profiles and early disease progression. Results from this profiling will ultimately lead to the development of a clinical test for early diagnosis of OSCC.

The application of pre-operative, neo-adjuvant chemotherapy or chemoradiotherapy has delivered significant improvements in disease free and overall survival in oesophageal cancer[7]. However, **not all patients respond equally well to all treatments**. ESR 2 (QUB recruit; TCD, ALMAC secondments) will undertake whole genome sequencing and microarray-based gene expression profiling of biopsies from early stage OAC to identify molecular signatures predictive of response to chemotherapy. Results from this profiling will ultimately lead to the **development of a clinical diagnostic test to predict responders and non-responders**.

The typically late diagnosis of oral cancer patients usually necessitates radiotherapy and surgical intervention. Lower inflammatory responses post-intervention are associated with successful recovery from cancer treatment. Monitoring the healing rate and control of inflammation is essential to aid in successful recovery. However, researchers and clinicians are currently unable to determine the effect of inflammation on wound healing, as the associated inflammatory profile is unknown. Thus, inflammatory profiles have the potential to be utilised as a measure of patient recovery, but there are **currently no clinical assays for monitoring inflammation during treatment**. ESR 3 (UVEG recruit; IME-SP secondment) will evaluate the levels of local inflammatory markers as an indicator of positive response to treatment in order to **determine specific inflammatory profiles linked to wound healing and develop assays to monitor toxicity, tumour control and patient recovery**. This project builds on the use of diagnostic tools developed in the Bagan lab which identified EGF as a discriminating factor in oral cancer[8]

Resistance mechanisms (WP3)

TRACT will uncover the molecular basis of drug resistance mechanisms in OOC with the aim of 1) improving the efficacy of existing therapies, 2) identifying new drug targets, and 3) developing novel therapies. Initial pre-clinical testing will be carried out to support future translation to clinical studies.

Current treatment strategies for OOC include a combination of surgery, radiotherapy and chemotherapy. **Chemotherapeutic treatment is currently impeded by drug resistance and a lack of selectivity**. A greater understanding of the cellular mechanisms that contribute to chemotherapeutic resistance in OOC will enable the **development of combination therapies with greater efficacy** than current chemotherapeutic regimes. Targeted combination therapies hold the promise of **improved response rates, decreased chemotherapeutic toxicity and enhanced survival rates**.

ESR 4 (QUB recruit; ALMAC, IME-SP, TCD secondments) will perform RNA-seq and microarray-based gene expression profiling on matched pre-chemotherapy endoscopic biopsies of early stage oesophageal adenocarcinomas and normal tissue resections. The resulting profiles will allow the **identification of differentially expressed/frequently mutated genes and associated molecular pathways in pathological responders and non-responders**, informing the design of **new therapies for OAC**. Preliminary data analysis has identified the MAPK and glycolytic pathways as potential targetable pathways. Determinants of drug resistance may also lead to the development of a **potential diagnostic test** to classify non-responders versus responders.

Recent research by Creagh in TCD has implicated inflammatory caspases as key mediators of intestinal inflammation and as biomarkers for colon cancer[9]. As OAC is an inflammation-associated cancer, ESR 5 (TCD recruit; QUB, OPSONA secondments) will conduct a study to establish whether inflammatory caspases may also represent biomarkers for early stage OAC. The involvement of inflammatory caspases in OAC development and resistance will also be examined using siRNA and inflammation/caspase inhibitors in OAC cell lines & *in vivo* models, ultimately leading to the **development of novel diagnostics for OAC, and assays for enhanced patient stratification, enabling more effective therapeutic choices**.

Drug resistance and a lack of selectivity impede current chemotherapeutics for OOC. Thus, **new therapeutic options for the treatment of recurrent OOCs are urgently needed**[10]. Cancer biology research has led to the

7 Sjoquist KM, et al., . Lancet Oncol. 2011 Jul;12(7):681-92.

8 Bagan et al., (2012) J Oral Pathol Med. 2012 Oct;41(9):662-6.

9 Flood, B. et al. (2015) Clin. Exp. Immunol.181, 39-50.

10 Da Silva, S.D. et al., (2012) Front Pharmacol. 3: 149.

selective inhibition of rate-limiting targets in the progression of many chemotherapy resistant cancers (e.g. Cetuximab (anti-EGFR) - colorectal cancer[11]; Bortezomib (Proteasome inhibitor) - multiple myeloma)[12]. Resistance to cell death is a common hallmark of cancer and is often mediated by the Bcl-2 family of proteins. Among all anti-apoptotic Bcl-2 members, Mcl-1 functions as a major survival factor, particularly in solid cancers. In the last year Mcl-1 has been identified as an important therapeutic target for OOC[13]. However, no specific Mcl-1 inhibitors exist. ESR 6 (UNISI recruit; Exosomics, TCD secondments) will **computationally design and synthesise Mcl-1 inhibitors** with the ability to sensitise OOC cells to apoptosis with appropriate pharmacokinetic properties. The agents will be tested in models of OSCC and efficacy of the novel compounds will also be determined by means of exosome content evaluation.

Pre-operative reduction of OOC tumour masses greatly improves patient survival post surgery. However, **current chemo- and radio-therapeutic strategies have undesirable long-term effects**. Full length and peptide fragments of the natural human milk protein α-lactalbumin non-covalently bound to oleic acid (a.k.a HAMLET) have proven effective in treating bladder and intestinal tumors with no observable side effects[14],[15]. The tumoricidal mechanism is multi-faceted (work by Mok in TCD and others[16],[17]), providing further opportunities to design targeted therapeutics. ESR 7 (TCD recruit; Oroboros & UNISI secondments) **will generate neo-adjuvant HAMLET therapy of enhanced efficacy** by chemically coupling oleic acid to a variety of α-lactalbumin peptides (UNISI). **Hamlet derivatives will be tested on OAC cell** lines, and the **mode of action studied by genome-scale CRISPR knockout[18] and next generation sequencing (TCD).** Metabolic changes will also be analysed by respirometry (OROBOROS).

Genetic and pharmacological screens have identified autophagic mediators as effective adjuvant and neoadjuvant targets. However, results from a recent phase 1 trial of the autophagy inhibitor hydroxychloroquine to treat newly diagnosed glioma patients demonstrated dose limiting toxicity[19]. Therefore, in order to exploit autophagic mediators as therapeutic targets, lower toxicity compounds are required. ESR 8 (UNISI recruit; Exosomics, TCD secondments) will carry out **bioinformatic screening to identify and develop new targets**. Novel compounds against promising targets will be rationally designed and synthesised, and **efficacy screening will be carried out in OSCC models**. **Efficacy of the novel compounds will also be evaluated by means of exosome content evaluation.**

Tumour resistance to therapy is related to the cell survival properties of autophagy and this pathway is frequently activated by chemotherapies in patients with various types of cancer. However, the **role of autophagy in OSCC remains unclear**, although preliminary studies in TCD have demonstrated that OSCC cell lines undergo autophagy in response to chemotherapy treatment. ESR 9 (TCD recruit; UVEG and Andor secondments) will investigate the expression of key autophagic regulatory proteins in OSCC patient samples and **correlate expression with clinicopathologic factors and overall patient survival**. ESR 9 will also **determine whether combining existing OSCC chemotherapy strategies with autophagy inhibition represents a better treatment strategy** for the benefit of OSCC patients.

Metabolic transformation (WP4)

TRACT will examine metabolic transformation mechanisms in OOC with the aim of identifying new drug targets for future therapeutic development. Metabolic transformation is a universal property of tumour formation and is a rich source of targets for development of therapeutic interventions[20]. Pilot studies performed in QUB using a pathways based approach to identify determinants of drug resistance in OOC have identified the glycolytic pathway as a potential targetable pathway. ESR 10 (Oroboros recruit; TCD secondment) will further **characterise the bioenergetic and metabolic differences in normal, dysplastic and cancerous oral cancer cells** using the Oroboros Respirometer Multisensor system and state-of-the-art Seahorse analysis. This approach will **identify differential novel drug targets** and means to **enhance the chemotherapeutic sensitivity of cancer cells**.

Factors that control mitochondrial dynamics in cancer cells have also emerged as possible therapeutic targets. The dynamic structure of the mitochondria in mammalian cells is defined by the opposing forces of fission and

11 Debucquoy A. et al., (2010) Clin. Cancer Res.16, 2709–2714
12 Mahindra A., et al., (2012). Nat. Rev. Clin. Oncol.9, 135–143.
13 Maji et al., (2015) Oncotarget, 6, 16623-16636.
14 Payton S. (2013) Nat Rev Urol. 10(3):126.
15 Puthia M, et al., (2014) Gut. 2014 Jan;63(1):131-42.
16 Storm P, et al., (2013) PLoS One. 2013;8(3):e58578.
17 Nadeem A, (2015) Sci Rep. 5:16432
18 Shalem O, (2014) Science. 343(6166):84-7.
19 www.uphs.upenn.edu/news/News_Releases/2014/05/hcq/
20 Smolková K, et al., (2011) Int J Biochem Cell Biol. 43:950-68.

fusion, but the **regulation of these mitochondrial processes is poorly understood**[21]. This is an emerging area in cancer research where cutting-edge imaging technologies are merging with molecular and cellular biology techniques. Pilot studies performed by Porter in TCD have identified a key molecule involved in controlling mitochondrial abundance (namely SIRT3) as a determinant of drug resistance in some solid cancers (manuscript in preparation). ESR 11 (TCD recruit; Oroboros secondment) will establish the **relationship between mitochondrial abundance, morphology, functional proteins involved in mitochondrial dynamics and metabolic differences in normal, dysplastic and oral cancer cells**. This new knowledge will lead to the **identification of novel therapeutic targets**.

Table 1.1b Delivering novel OOC diagnostics and therapeutics through integrated ESR research programme

ESR	Project Title	Research Objectives/Clinical Need
1	Inflammatory response elements and glycan profiles as salivary biomarkers for the early diagnosis of OSCC	Biomarker Discovery/Diagnostic
2	Identification of novel molecular biomarkers predictive of benefit to neo-adjuvant chemotherapy in OAC	Biomarker Discovery/Diagnostic & Therapeutic
3	Modulation of salivary inflammatory markers in patients undergoing radiotherapy for OSCC	Biomarker Discovery/Diagnostic & Therapeutic
4	A pathways-based approach to identify determinants of drug resistance in OAC	Resistance Mechanisms/Diagnostic & Therapeutic
5	Inflammatory caspases as biomarkers for OAC? Determining the role of inflammatory caspases in OAC development and resistance	Resistance Mechanisms/Diagnostic & Therapeutic
6	Mcl-1 inhibitors for the treatment of OSCC	Resistance Mechanisms /Therapeutic
7	HAMLET derivatives as a pre-operative therapy in OAC	Resistance Mechanisms / Therapeutic
8	Development of novel autophagy modulators to improve sensitivity of OSCC to chemotherapy	Resistance Mechanisms / Therapeutic
9	Pre-clinical evaluation of targeting autophagy for the treatment of OSCC	Resistance Mechanisms / Therapeutic
10	Metabolic profiles in normal, dysplastic and cancerous oral cells	Metabolic Transformation/ Diagnostic & Therapeutic
11	Mitochondrial function linked to metabolic differences in normal, dysplastic and cancerous oral cells	Metabolic Transformation/ Therapeutic

1.1.5 Originality & innovative aspects of the research programme

The past decade has witnessed a renewed appreciation of the complexity of cancer cell metabolism, survival and therapeutic resistance. These characteristics are especially important in the context of OOC, which is difficult to detect, is frequently diagnosed late, has few therapeutic options and has poor survival rates. Current state of the art in clinical diagnosis is limited to visual/endoscopic examination of the oral/oesophageal region and histological analysis of tumour biopsies. In addition, the predominant treatment approach is neo-adjuvant chemotherapy/radiotherapy followed by surgery. The TRACT project will focus on developing **original and innovative solutions to key challenges in OOC diagnosis and treatment** through the development of methods for early and accurate diagnosis, methods for monitoring patients during therapy, approaches for prognostic stratification of patients, novel therapeutics to overcome resistance and novel target pathways, including metabolic transformation pathways. The consortium will also look to build on the advances of other funded European projects, such as GlycoHIT. This FP7-funded project, of which NIBRT was a partner, developed technologies that enable fast and accurate analysis of glycosylation in blood samples from cancer patients. TRACT will build on the findings and expertise developed by NIBRT during the project. Currently, scientists working in the area of oral cancer research, diagnosis and therapeutic development receive **restricted training in specific disciplines**. This narrow approach limits the innovation potential of OOC basic and applied research in both academic and non-academic settings. There are currently no multidisciplinary doctoral training programmes focussed on OOC. There is an oesophageal cancer network, the OCCAMS network based out of Cambridge[22], but it is primarily a sequencing project for the International Cancer Genome Consortium and is not involved in doctoral training. The TRACT approach is unique in that it is focused on biomarker and novel therapeutic, prognostic and diagnostic development and their translation into clinical practice which is something the OCCAMS group have not done to date. TRACT will advance the state-of-the-art by integrating multidisciplinary, intersectoral research with outputs from cutting-edge technologies including next-generation whole genome sequencing, RNA-seq

21 Chan D.C. (2012) Annual Review of Genetics 46: 265-287

22 http://www.mrc-cu.cam.ac.uk/research/rebecca-fitzgerald/clinical-studies/occams

analysis, CRISPR technology, 2-D NMR metabolomics, exosome analysis, Seahorse bioenergetic analysis, in vivo imaging, and in-silico drug screening. **Therapeutic benefits from the research programme are promising since potential molecular drug targets and biomarkers have already been identified by pilot studies.**

1.1.6 Gender aspects of the research programme

Oral cancer historically has a high male to female ratio in terms of incidence. In a case study of 1564 diagnoses, the gender difference was calculated as 2.8:1 males to females[23]. Explanations include a greater propensity for men to engage in high-risk habits, as noted in a study carried out on people < 45 years of age, which showed large gender differences in common oral cancer risk factors, such as cigarettes and alcohol use[24]. However, more recent data and reports show a convergence of decreasing male and increasing female incidence rates of major tobacco related cancers including OSCC[25]. In particular, eastern and central European regions show increased female incidence rates of oral cancer mostly due to increased alcohol and tobacco consumption by females whilst rates in males remained static[26,27]. Thus, TRACT research is vital for the future health of both young European women and men. Consideration of sex/gender differences in differential responses within clinical patient samples will be integrated into the research. For example, gender differences will be examined in studies to identify responder/non-responder groups.

1.2 Quality and innovative aspects of the training programme

1.2.1 Overview and content structure of the training

TRACT proposes a high-level, joint research-training programme that focuses on exploiting the research expertise and infrastructure of all the beneficiaries and associated partners, availing of complementarity with programmes offered locally at participating institutions and promoting scientific excellence and innovation. Specifically, the TRACT training programme includes mechanisms to:

- **Develop research-related competencies** in the area of cancer research in a cohort of ESRs under three research themes (Biomarker Discovery, Resistance Mechanisms and Metabolic Transformation) through carefully supervised individual research projects,
- **Extend the traditional academic research training environment** to include exposure to private sector research and development activities through secondments and intersectoral training events,
- **Equip a cohort of ESRs with the skills needed to translate basic research findings** into future products and services, with a particular focus on clinical translation for patient benefit,
- **Foster a multidisciplinary mindset to enable more effective innovation** through a programme of structured knowledge exchange (conferences, workshops) and networking,
- **Widen the perspectives of the participating ESRs on future careers** in both academic and non-academic sectors through secondments and intersectoral training events,
- **Provide a career development plan for participating ESRs** (see section 1.3.2 for more details),
- **Promote international, interdisciplinary and intersectoral mobility** through exposure to a range of working environments, and
- **Exploit complementarity with programmes offered locally** at participating institutions ("Innovation Academy at TCD, 'Computational Biology' and 'Generic Skills in Communicating Science' workshops at QUB, etc.).

The TRACT **training objectives** are to:
1) Train ESRs in techniques relevant to cancer biomarker discovery, drug discovery and validation, and assessment of cellular metabolic changes, including whole genome sequencing, RNA-seq analysis, high-throughput glycoarrays, metabolomics, real-time Seahorse respiration technologies, advanced imaging, CRISPR generated cancer models, exosome analysis, medicinal chemistry, bioinformatics and systems biology techniques.
2) Provide ESRs with a solid foundation in commercialisation to improve links between industry and research organisations in order to drive more rapid and effective translation of research findings into products that will enhance cancer diagnosis and management for the benefit of patients and the European life sciences industry.
3) Train ESRs in transferable skills relevant for future academic and non-academic careers, including entrepreneurship, project management, communication, management of Intellectual Property, ethics, scientific writing and personal development planning.

The training objectives will be achieved through **Table 1.2a Recruitment Deliverables per Beneficiary**

23 Marocchio, L.S., et al., J Oral Sci, 2010. 52(2): p. 267-73.
24 Llewellyn, C.D., et al., Oral Oncol, 2004. 40(3): p. 304-13.
25 Lortet-Tieulent et al. Eur J Cancer. 2013 Nov 20. pii: S0959-8049(13)00952-0.
26 La Vecchia et al., Oral Oncol. 2004 Apr;40(4):433-9.
27 Garavello et al., 2010 Jul 1;127(1):160-71.

individual, project-specific training undertaken by each ESR at their recruiting institution (Table 1.2a) and through participation in two parallel, project-wide training streams devoted to scientific and complementary skills (Table 1.2b). In this way, all ESRs will benefit from the expertise and experience of their recruiting and secondment institutions, as well as from that of the consortium as a whole. All ESRs will be registered to a PhD programme. ESR 10 (based at the SME Oroboros) will be registered for a PhD at the Medical University of Innsbruck, where the Oroboros CEO (Erich Gnaiger) is also a lecturer. Supervision arrangements are detailed in section 1.3.2.

Researcher No.	Recruiting Participant (short name)	Planned Start Month (0-45)	Duration (months, 3-36)
ESR 1	UVEG	6	36
ESR 2	QUB	6	36
ESR 3	UVEG	6	36
ESR 4	QUB	6	36
ESR 5	TCD	6	36
ESR 6	UNISI	6	36
ESR 7	TCD	6	36
ESR 8	UNISI	6	36
ESR 9	TCD	6	36
ESR 10	OROBOROS	6	36
ESR 11	TCD	6	36
Total: 11			

Table 1.2b Main Network-Wide Training Events, Conferences and Contribution of Beneficiaries
([C] Compulsory Attendance; [E] Elective)

	Main Training Events & Conferences	ECTS	Lead Institution	Project Month
1	Kick-off Meeting (includes Introduction to OOC, Research Integrity, Gender/Sex in Research/ Open Science)[C]		TCD	6
2	Tumor histology[E]		TCD	6
3	Antibody technology in cancer research and therapy[E]		TCD	6
4	Animal models in cancer research and drug discovery[E]		TCD	6
5	Whole body imaging in xenograft cancer models[E]		TCD	6
6	Drug discovery & medicinal chemistry[E]		UNISI	6
7	Biomarker discovery[E]		UVEG	6
8	Cancer cell metabolism[E]		Seahorse	12
9	Training in mitochondrial and cellular respiratory physiology[E]		Oroboros	12
10	Generic skills in communicating science[C]		QUB	18
11	Fluorescence and electron microscopy imaging of cells[E]		Andor	18
12	Computational Biology[E]		QUB	18
13	Year 1 Meeting[C]		QUB	18
14	Outreach event for OOC patient/advocacy groups[C]		QUB	18
15	NMR Mini Boot Camp of BioBank Analyses and Metabolomic Transformation in Cancer[E]		TCD	24
16	Analytical techniques in glycobiology[E]		NIBRT	24
17	Project management targeted to industrial needs[C]		NIBRT	24
18	Innovation Academy & Career Development Workshop (includes Gender Issues, WiseR)[C]	30	TCD/QUB	24, 30, 36
19	Year 2 Meeting		TCD	26
20	TRACT Marie Sklodowska-Curie ITN Open Day/Exploitation Workshop[C]		TCD	36
21	Closing Symposium[C]		UNISI	45

1.2.1.1 Scientific Training

Scientific Methods: Training in general scientific methods will be carried out locally, through both hands-on and classroom-based training, delivered by the primary supervisor and the recruiting institution. Training will be tailored to the previous experience of each ESR, and will be carried out on an on-going basis. Key topics include:

- **Laboratory safety training** - site-specific procedures (evacuation, waste disposal, etc.), risk assessments, etc.
- **Research planning** - performing literature searches, critically reviewing publications, etc.
- **Experimental design** - planning research experiments through development of clear objectives and experimental design (design of appropriate controls, etc.).
- **Data collection** - how to record data in a notebook, how to manage electronic data, etc.
- **Data analysis** - critical evaluation of scientific data, statistical analysis, etc.

Technical Methods: TRACT ESRs will also receive technical training in a) methods specific to the individual ESR research projects, and b) methods common across the three TRACT research themes. Training in project-specific methods will be delivered locally under the direction of the Primary Supervisor and Secondary Supervisor. Training in project-wide methods will be delivered through a series of workshops held throughout the project (see

workshops described below and Table 1.2b). ESRs will be required to attend four elective training events, which they will select with their Support Team and specify in their **Personal Development Plan** (section 1.3.2). At M6, all ESRs will receive initial training in TCD over a two-week period coinciding with the Kick-off Meeting:

'Tumour Histology' (Organiser: TCD; **Duration:** 2 days**):** This course will familiarise students with histology and its use in tumour grading and tissue of origin determination. Hands-on-experience in tissue sectioning, tissue embedding, immunohistochemical (IHC) staining and H&E staining will be provided using tumour samples recovered from the xenograft workshop. This course will also be open to wider research community.
'Antibody Technology in Cancer Research and Therapy' (Organiser: TCD; **Duration:** 2 days**):** A local specialist training course in antibody technologies will be delivered at TBSI where ESRs will attend lectures on the theory of antibody technologies and therapeutics widely used in cancer research and in the clinic. A series of practicals will also be given as part of the workshop, where ESRs will perform experiments using each of these technologies.
'Animal Models in Cancer Research and Drug Discovery' (Organiser: TCD; **Duration:** 2 days**):** This event will include four lectures on the use of animals in cancer research: xenograft, transgenic, gene-targeted and CRISPR generated cancer models and the technologies that have been developed to evaluate and analyse tumour status. Students will gain hands-on-experience, of benefit for subsequent training events (see below). TBSI is equipped with a state-of-the-art transgenic facility, *in vivo* animal imaging capabilities (with multiphoton intravital microscope), histology suite, MoFlo 4-Color High Performance Cell Sorter and an 800 MHz NMR spectrometer.
'Whole Body Imaging in Xenograft Cancer Models' (Organiser: TCD; **Duration:** 2 days**):** *In vivo* live imaging of tumour xenografts has become a key technology to understanding cancer development and metastasis and in the evaluation of cancer therapeutic drugs. Students will have the opportunity to carry out imaging of xenograft animals, and evaluate and quantitate the growth over time. This course will also be open to wider research community.
'Drug Discovery and Medicinal Chemistry' (Organiser: UNISI; **Duration: 2 days):** This workshop will cover the principal discovery and development phases of small drug molecules. Topics covered will include: target selection; biochemical and computational strategies of molecular design; optimisation and selection processes; pharmacokinetic and toxicological assays used to inform transition to phase I trials. This course will also be open to wider research community.
'Biomarker Discovery' (Organiser: UVEG**; Duration 2 days):** This course will examine the need and potential for novel biomarker discovery in a clinical setting. ESRs will receive structured training in current genomic, proteomic and glycomic biomarker discovery theory and techniques. The workshop will also provide grounding in the use of bioinformatics and analytical tools in biomarker validation. This course will also be open to wider research community.

At M12, 18 and 24, relevant ESRs will be able to attend project-wide workshops hosted locally as detailed below:

M12
'Cancer Cell Metabolism' (Organiser: Seahorse; **Duration:** 2 days**):** Metabolic transformation is a universal property of tumour formation and a promising mode of treatment. Through state-of-the-art Seahorse analysis ESRs will learn about the alterations in metabolism that sustain cancer cell growth and resistance to therapy.
'Training in Mitochondrial and Cellular Respiratory Physiology' (Organiser: Oroboros; **Duration:** 3 days**):** Oroboros will provide O2k- Workshops to TRACT ESRs on use of the Oxygraph-2k respirometer to measure oxygen consumption rates, transmembrane potential differences using TPP-electrodes and fluorescence sensitive electrodes to determine hydrogen peroxide production (Amplex red), membrane potential (Safranin), ATP production (Mg green) or Ca2+ (Ca green).
M18
'Fluorescence and Electron Microscopy Imaging of Cells' (Organiser: Andor/TCD; **Duration:** 4 days**):** This training course will consist of a placement on the Andor Academy level three training programme at the Andor facility in Belfast. This element will cover topics in advanced light microscopy and will take two days. The CMA/TBSI in TCD will run a two-day workshop on the use and application of electron microscopy for biological imaging.
'Computational Biology' (Organiser: QUB; **Duration:** 3 days**):** In this training course ESRs will be given a systematic introduction to quantitative analysis methods for high-throughput data which is needed to analyse genomics data from biology and cancer biology. This course will also be open to wider research community.
M24
'NMR Mini Boot Camp of BioBank Analyses and Metabolomic Transformation in Cancer' (Organiser: TCD; **Duration:** 2 days**):** TCD's TBSI are developing 2D NMR metabolomics methodologies. This training course will be targeted to provide the ESRs (as well as to others in the medical, pharma, and bio research sectors): (1) lectures introducing the underlying principles and practices of modern NMR spectroscopy, with (2) hands-on experience to be able to run and analyse biomolecular samples.
'Analytical Techniques in Glycobiology: Applications to biomarker discovery' (Organiser: NIBRT; **Duration:** 3 days**):** This course will be run by NIBRT in their research facilities in Dublin and specifically trains researchers in biomarker discovery and validation. The focus will be on glycan biomarkers and blood samples from cancer patients will be analysed during the 3-day course. Complex HPLC and MS techniques will be presented to TRACT researchers who will carry out sample clean-up experiments, derivatization procedures, HPLC analysis and interpretation of results using established in-house database systems (GlycoBase).

Research Ethics & Integrity: As part of their local induction training, all ESRs will be trained on recognised ethical practices and fundamental ethical principles relevant to their discipline(s), as well as to ethical standards as documented in the different institutional Codes of Ethics. In addition, at the first project meeting (M6), TRACT researchers will receive instruction from Prof Orla Sheils, Chair of TCD Research Ethics Committee, on matters such as informed consent, social/cultural impact of research and research integrity. Training in research integrity will ensure research is performed according to the highest standards of professionalism and rigour, and ensure the accuracy and integrity of the research record in publications and elsewhere.[28]

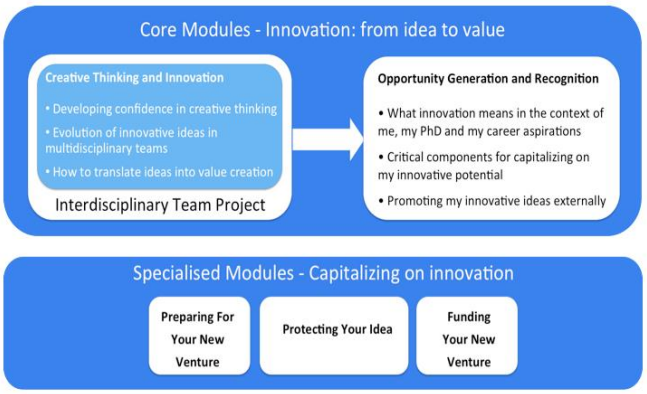
Gender/Sex in Research: Sex/gender differences may impact on the research planned in TRACT. Training by Yellow Window, an FP7-funded initiative, will be compulsory for all TRACT ESRs and will be delivered at the 'kick off' meeting. This training includes a practical toolkit on how to consider gender in all aspects of research. ESRs will also learn about the role of gender/sex in research through their individual projects. For example, gender differences will be examined when analysing responses to chemotherapy or assessing drug resistance.

Open Science: Niamh Brennan from TCD is a consortium member of OpenAIRE, a H2020 funded project on open science and will deliver a session at the introductory meeting.

1.2.1.2 Complementary Skills Training

Innovation: TRACT ESRs will receive training from the Innovation Academy (www.innovationacademy.ie) at M24, 30 and 36. The Innovation Academy was established in 2010 by TRACT Coordinator TCD, in collaboration with University College Dublin and TRACT partner QUB, with a mission to transform PhD graduates into energetic and resourceful entrepreneurs with the requisite skills to pursue fresh ideas and new ventures. Innovation Academy modules completed by the TRACT ESRs can be applied towards a **Postgraduate Certificate in Innovation & Entrepreneurship**, giving them formal recognition of their transferable skills training. Modules include:

- Module 1 (2 weeks) - *Creative Thinking and Innovation* (10ECTS) aims to ignite creative thinking in early stage researchers, with an emphasis on building foundations of non-discipline specific innovation as part of multi-disciplinary teams.
- Module 2 (1 week) - *Opportunity Generation and Recognition* (5ECTS) aims to aid in the ESRs' identification and assessment skill-sets required to develop ideas related to their individual projects. Upon completion, ESRs should be able to develop and assess the most innovative aspects of their PhD thesis research, as well as identify potential pitfalls to further development and implementation and develop a strategy to navigate these pitfalls. A key outcome of the module is a 'researcher pitch' video.



Structure of the Postgraduate Certificate in Innovation & Entrepreneurship

- Module 3 (1 week) - *Protecting Your Idea, Novelty, Copyright and Intellectual Property* (5ECTS) introduces ESRs to quality, early identification and protection of IP, including an exploration of copyright, patenting, trademarks, industrial design and know-how as well as ways of deriving value from the 'unprotectable'.
- Module 4 (1 week) - *Planning Your New Venture* (5ECTS) This module will provide an understanding of the components of a comprehensive business plan for a new venture and the ESRs will examine the potential problems that may be encountered in developing a business plan.
- Module 5 (1 week) - *Creative Capital: Financing Your New Venture* (5ECTS) ESRs will learn how to evaluate the financial performance, financial position and cash flow of an enterprise and be able to identify target areas to consider whilst seeking finance for a new venture.

Project Management: All ESRs will complete a formal, two-day workshop **'Project Management Targeted to Industrial Needs'** run by industrial partner NIBRT. The formal training will consist of a two-day training course with a focus on project management in industrial settings. Topics covered will include writing project proposals/business plans, recruitment, outsourcing, safety and regulatory issues, costing, project management tools, meeting deadlines and setting up contingency plans.

[28] http://www.iua.ie/research-innovation/research-integrity/.

In addition, all ESRs will receive hands-on training for managing their individual research project. Hands-on project management training will focus on management of academic research projects, and will be delivered by the Primary Supervisor of each ESR on an on-going basis over the project. The training will include regular planning and progress meetings, with ESR reports at M18, 30 and 42 as formal outputs.
Finally, all ESRs will collaborate to organise a **'TRACT Marie Sklodowska-Curie ITN Open Day and Exploitation Workshop'** at M36 to help them develop project management and event organisation skills (see section 2.4).
Communication/Outreach: All ESRs will be involved in, at minimum, two outreach activities per year over their three year appointments and the activities chosen will be included in each ESRs' PDP.
At M18, all ESRs will attend a two-day workshop in **'Generic Skills in Communicating Science'**, including modules entitled 'Writing a PhD Thesis', 'Writing a Good Scientific Paper', 'Critiquing a Research Paper' and 'Giving a Research Talk'. This workshop has been developed by the Centre for Cancer Research and Cell Biology (CCRCB) in QUB and is currently delivered to all QUB postgraduate students. ESRs will be given multiple opportunities to apply the workshop learnings though presentations at TRACT project meetings, involvement in public engagement outreach activities with a focus on communicating science to the general public and attendance at external academic conferences. In addition, in conjunction with the M18 project meeting, all ESRs will present their research to a lay audience at an **outreach event for OOC patient/advocacy groups,** organised by QUB and chaired by Dr. Richard Turkington (QUB) (see section 2.4 for further details).

At M45, the project will host a two-day **'Closing Symposium'** at UNISI. Attendees will include all ESRs and supervisory personnel involved in the project, as well as interested researchers and industry representatives from a variety of related fields, such as drug discovery and diagnostics. The symposium will include oral presentations by all ESRs. In addition, the Principal Investigators (PIs) will lead discussion sessions on exploitation of project findings, including the presentation of market research and business plans by the ESRs. The discussion sessions will promote the future commercial development of novel biomarkers and chemical/biological therapeutics arising from the project through our industrial partners.

Teaching/Training: ESRs will be involved in teaching and training activities through their recruiting institutions, including laboratory demonstrating, tutorials/seminars, undergraduate project supervision and supervision of technical staff. These activities will be overseen by the Primary Supervisors and will be detailed in each ESRs' PDP.

Gender Issues: All ESRs will receive training by Prof Eileen Drew of Women in Science & Engineering Research (WiseR) as part of the Career Development Workshops at M24. WiseR is an initiative, partly funded by FP7, which works to 'recruit, retain, return and advance' women in academic science, engineering & technology (SET). Training will include networking/building a research profile and maintaining work/life balance. WiseR will also advise researchers on how to influence policy in their own institution in a range of areas, such as representation of women in senior positions and flexible working arrangements. In addition, a speaker from the Research Centre for European Integration, a Jean Monnet Centre of Excellence hosted by UNISI, will deliver a session on gender quality in the public sector to all ESRs at the project meeting at M45.

1.2.1.3 Career Planning

Upon completion of the project, ESRs will have developed skills that will enable them to pursue **careers in academia, industry or as entrepreneurs.** TRACT will include career planning activities, including:

- **Career development workshops** - will be held in conjunction with the Innovation Academy modules and will focus on CV preparation and interview skills, effective networking, job-seeking strategies and proposal writing/securing funding,
- **Supervisory Board member presentations** - academic and non-academic representatives will share their career paths and tips for success,
- **External keynote speakers** - successful researchers, including successful life science entrepreneurs, will be invited to present at project-wide meetings.

1.2.1.4 Multidisciplinary and Intersectoral Exposure

One of the intents of TRACT is to expose ESRs to a wide range of disciplines and sectors involved in cancer research and development. This will be achieved through the multidisciplinary nature of the individual research projects and the intersectoral secondments, but a wider exposure will also be achieved through annual project-wide meetings, held at M6, 18 and 30, and the **'Closing Symposium'** held at M45. The '**Kick-off Meeting'** at M6 will include presentations from all PIs on the state-of-the art of their subject area. A workshop entitled 'An Introduction to Oral and Oesophageal Cancer' will be given by PIs from UVEG and QUB and will provide ESRs with an up-to-date review of the current practises in the diagnosis and treatment of OOC and problems associated

with current treatments. In order to minimise travel expenses, various partners will deliver elective workshops in TCD over a two-week period directly following the Kick-off meeting (section 1.2.1.1). At the **"Year 1 Meeting'** in M18 and the **'Year 2 Meeting'** in M26, all ESRs will present oral presentations on their research. In addition to formal presentations, time will be devoted to workshops and discussion sessions where the impact of individual projects on the direction of the research programme as a whole can be explored. Presentations from Supervisory Board members and external keynote speakers will also be included to support career planning.

1.2.2 Role of non-academic sector in the training programme

The non-academic sector has a key role in TRACT in delivery of both the research/training elements of the programme and overall project oversight. Non-academic **research involvement** includes hosting secondments and ESR recruitment (OROBOROS), on-going review of emerging research results to identify new opportunities for innovation and involvement in IP identification and management through initial submission of invention disclosure forms. **Training involvement** includes delivery of formal training workshops as presented above (Cancer Cell Metabolism (Seahorse), Training in Mitochondrial and Cellular Respiratory Physiology (OROBOROS), Exosome-based Drug Discovery (Exosomics), Fluorescence and Electron Microscopy Imaging of Cells (Andor), Project Management Targeted to Industrial Needs (NIBRT)). Through participation in the Career Development Workshops held in conjunction with the Innovation Academy at M24, 30 and 36, industrial representatives will identify career opportunities for qualified researchers in their respective industries. Non-academic participants will also contribute to **project oversight** through representation on the Supervisory Board and regular consultations with the management of all our industry partners.

1.3 Quality of the supervision

1.3.1 Qualifications and supervision experience of supervisors

The combined supervisory experience in TRACT is excellent. Academic Primary and Secondary Supervisors have supervised a total of 165 PhD students to completion, and are leading experts in their respective fields:

PI	Expertise & Publications	Supervision Experience & Leadership Roles	ESR
Prof. Jose Bagan, MD, DDS, PhD (UVEG)	Oral medicine and pathology, discovery of novel biomarkers for treatment of OSCC; 326 publications	43 PhDs completed; 3 PhDs in progress; Head of Stomatology and Maxillofacial Surgery; Coordinator of Doctoral Programme in Clinical Dentistry; Director of research and teaching at University General Hospital in Valencia; Director of the School of Doctoral Programmes for UVEG	1, 3
Prof. Richard Kennedy, MB, BAO, Bch, BSc, PhD, FRCP (QUB)	Medical oncology and drug discovery, 90 publications	10 PhDs completed; 6 PhDs and 4 clinical fellows in progress; Director for undergraduate academic training in medicine	2, 4
Dr Richard Turkington, MB BCh BAO, BSc, PhD, MRCP	Medical Oncology and Upper-gastrointestinal cancer, 13 publications	1 PhD and 1 Clinical Fellow in progress. Director of the Academic Foundation Program	2,4 (Co-Supervisor: Kennedy)
Prof. Emma Creagh, B.A Mod, PhD (TCD)	Cancer inflammation; 24 publications	3 PhD/2 MSc completed; 1 PhD in progress; Co-ordinator of Freshman Biochemistry teaching	5, (Co-Supervisor: Murray)
Prof. James Murray, BSc, PhD (TCD)	Enzymology and metabolism; 30 publications	5 PhD/2 MSc completed; 2 PhDs in progress; Coordinator of Undergraduate Erasmus Exchange programme	5,
Prof. Giuseppe Campiani, MSc, PhD (UNISI)	Medicinal chemistry; 154 publications	28 PhDs completed; 4 PhDs in progress; Director of European Research Centre for Drug Discovery and Development; Rector's Delegate for International Cooperation & Development.	6, 8
Prof. Vincent Kelly, B.A. Mod, PhD (TCD)	Cancer biology; 23 publications	6 PhDs/1 MSc completed; 2 PhDs in progress; Coordinator of Molecular Medicine Undergraduate Degree; Director of the Transgenic Unit in TCD	7, (Co-Supervisor: Mok)
Prof. Mok, PhD (TCD)	Structural biology and NMR metabolomics; 47 publications	3 PhDs completed; 2 PhDs in progress; Director of TBSI NMR Facility	7

Prof. Daniela Zisterer, PhD (Coordinator, TCD)	Cell death mechanisms, development of anti-cancer therapeutics; 70 publications	15 PhDs completed; 2 PhDs in progress; Director of Research for School of B & I; Biochemistry Undergraduate Degree Coordinator; Coordinator of cancer stream of PRTLI funded structured PhD training programme (2011-2015)	9 (Co-supervisor O'Sullivan)
Prof. Jeffrey O'Sullivan, BSc, PhD (TCD)	Oral cancer; 19 publications	8 PhDs (Clinical Dentistry)/3 PhDs completed; 5 PhDs in progress; Coordinator of Biochemistry Teaching to Undergraduate Dental Science Students	9
Prof. Erich Gnaiger, PhD (OROBOROS)	Mitochondrial physiology & pathology; 82 publications	10 PhDs completed; 3 PhDs in progress; Organiser of > 90 international workshops on high-resolution respirometry	10
Prof. Richard Porter B.A. Mod, PhD (TCD)	Metabolism and bioenergetics; 45 publications	7 PhDs/2 MSc completed; 3 PhDs in progress; Head of Biochemistry in Trinity Biomedical Sciences Institute; Coordinator of Biochemistry Teaching to Undergraduate Medical Students	11

Non-academic supervisors also have significant experience in leading large teams of PhD level scientists. For example, Dr. Tim Davison from Almac Diagnostics has led teams of 17 PhD/11 MSc level scientists over the last 9 years. Many partners from the non-academic sector also have current and/or previous involvement in doctoral programmes. Notably, Andor and NIBRT are currently supervising ESR secondments from the FP7-funded ITN TINTIN (see Capacities Tables in section 5 for more detail).

1.3.2 Joint Supervision Arrangements - Academic/Non-Academic Collaboration

Each ESR will be supervised by an ESR Support Team, consisting of the Primary Supervisor from the recruiting, institution, a Secondary Supervisor(s) from each secondment-hosting institution and a Mentor (independent PI in the recruiting institution). The **Support Team will include both academic and non-academic representation**. As recommended by the European Charter for Researchers, the Mentor will provide support and guidance for personal and professional development, with a particular focus on transferable skills and career planning.

All ESRs will meet with their Support Team when they join the project at M6 to devise a Personal Development Plan (PDP). The PDP will detail the training they will receive throughout the programme and mechanisms for on-going assessment of progress. Each ESR will meet weekly with their Primary Supervisor when at the recruiting institution and the relevant Secondary Supervisor while on secondment. Monthly meetings will take place between ESR and their full Support Team (virtually or face-to-face). The Primary and Secondary Supervisors will have overall responsibility for introducing the ESR to their institute and the goals of the training programme, maintaining open lines of communication, co-developing an effective PDP with the ESR and providing timely feedback and support. A copy of the PDP will be sent to the project Supervisory Board for approval along with regular (six monthly) updates so that the Supervisory Board can monitor progress and provide constructive feedback. ESRs will receive informal feedback following each monthly meeting with their Support Team. Formal feedback will be provided to ESRs following their presentation at the annual meeting.

1.4 Quality of the proposed interaction between the participating organisations

1.4.1 Contribution of all participants to the research and training programme

The aim of TRACT is to **train a cohort of ESRs** to use the expertise and state-of-the-art technology contributed by all participants **to research cancer cell mechanisms** and to **discover new methods for OOC detection and treatment.** The programme has been designed so that all participants contribute to both research and formal/informal training activities (Table 1.4a). In addition to specific interactions with ESRs working within their institutions, TRACT participants will **contribute multidisciplinary and intersectoral knowledge** in bioenergetics (Seahorse, Oroboros), exosomes (Exosomics), cell imaging (Andor), bioinformatics (Almac Diagnostics, UNISI), biomarkers (UVEG, QUB, Almac

Table 1.4a Contribution of all participants to TRACT

Participant	Recruitment & Hosting of ESR	Hosting ESR Secondment	Provision of training workshop
TCD	√ (ESR 5,7,9,11)	√(ESR 2,4,6,8,10	√
QUB	√ (ESR 2,4)	√ (ESR 5, 7)	√
UNISI	√ (ESR 6,8)	√ (ESR 7)	√
UVEG	√ (ESR 1,3)	√ (ESR 9)	√
OROBOROS	√ (ESR 10)	√ (ESR 7, 11)	√
Almac Diagnostics		√ (ESR 2,4)	
Andor		√ (ESR 9)	√
Exosomics		√ (ESR 6,8)	
IME-SP		√ (ESR 3,4)	
NIBRT		√ (ESR 1,3)	√
Seahorse			√
Opsona		√ (ESR 5)	

Diagnostics, NIBRT), immunotherapeutics (TCD, Opsona) and drug discovery (UNISI, IME-SP, Exosomics) to all ESRs through project-wide meetings. Participants will also provide **access to a broad range of technologies** such as through project-wide meetings. Participants will also provide access to state-of-the-art technologies such as genome scale CRISPR knockout and next generation sequencing, metabolomics, Seahorse bioenergetic analysis, *in vivo* imaging and *in-silico* drug screening.

1.4.2 Synergies between participants

Partnerships between industry and academia enhance the strengths of both partners and provides access to resources and expertise neither party could achieve alone. Key to the success of the partnerships in TRACT is the principle of knowledge transfer, whereby ESRs are able to draw experience from both high quality environments.

TRACT builds on previous and on-going collaborations between a number of consortium partners, which leverage complementary expertise. For example, Almac Diagnostics was originally formed as a spin-out company from the Centre Cancer Research and Cell Biology (CCRCB) at QUB. As a leader in biomarker development, Almac Diagnostics have developed a rigorous approach to the analysis of genomic data for the identification of novel diagnostics. This involves expertise in project management, quality assurance and design control, with a focus on advancing biomarkers to meet current regulatory standards. A long standing collaboration (21 years) has also existed between Zisterer in TCD and Campiani in UNISI. Principally, UNISI, experts in medicinal chemistry, have provided novel drugs to TCD for biological evaluation. UNISI and TCD hold a joint patent as a result of this collaboration and have jointly published 35 research articles.

1.4.3 Exposure of recruited researchers to different research environments

All ESRs will be recruited or seconded to both academic and non-academic environments. Furthermore, secondments for each ESR have been specifically designed to avail of industry expertise, facilitating complementary advanced training in specialised technologies, exchange of knowledge and ideas and meaningful exposure to different research environments.

Table 1.4b Secondments of ESRs to academic and non-academic partners

ESR No	Host Beneficiary (Academic/SME)	Secondment(s) (non-academic)	Secondment (academic)
1	UVEG (academic)	NIBRT	
2	QUB (academic)	Almac Diagnostic	TCD
3	UVEG (academic)	IME-SP	
4	QUB (academic)	IME-SP & Almac Diagnostic	TCD
5	TCD (academic)	Opsona	QUB
6	UNISI (academic)	Exosomics	TCD
7	TCD (academic)	OROBOROS	UNISI
8	UNISI (academic)	Exosomics	TCD
9	TCD (academic)	Andor	UVEG
10	OROBOROS (SME)		TCD
11	TCD (academic)	OROBOROS	TCD

2. Impact

2.1 Enhancing the career perspectives and employability of researchers and contribution to their skills development

Research excellence is the fundamental principle on which TRACT is built. Eleven novel research projects are proposed, which will challenge ESRs to push the boundaries of the research field under the guidance and supervision of experienced clinicians and leading researchers from multiple disciplines. Interactions with the non-academic sector is also embedded in both research and training aspects of the programme, enabling ESRs to receive intensive training in advanced technologies. TRACT research and training activities will benefit the careers of the participating fellows in a number of ways.

Intersectoral and multidisciplinary skills and perspectives: The doctoral training achieved through TRACT will exceed traditional PhD training. TRACT ESRs will benefit from exposure to an array of disciplines and sectors, regardless of their intended, future career paths. The research training will allow ESRs to develop discipline-specific skills through hands-on research and training courses. Secondments, training events and project-wide meetings will expose them to real-world applications of basic research and how research is brought to the clinic and market. Fellows trained through the TRACT network will be **uniquely positioned for careers in academia, industry or as entrepreneurs**. The interdisciplinary nature of the project will give them access to the collaborative expertise of clinicians, biochemists, immunologists and chemists, so that the TRACT cohort of researchers will be able to communicate across scientific disciplines. Involvement of the non-academic sector in governance,

supervision of projects, training and hosting of secondments will ensure network ESRs will be able to work across the public-private divide, for example through research collaborations between universities and industry.

Impact on academic career prospects: Oral and oesophageal cancer are one of the few cancers which are increasing in incidence, particularly among women (see Section 2.2.2). This, together with the multidisciplinary approach and the highly innovative techniques such as CRISPR technology that the ESRs will be exposed to, will position graduates of this programme to become research leaders and also to potentially inform the development of academic curricula. They will be equipped with skills to develop their own ideas and will have a broader perspective, making them more competitive for academic positions. It is expected that the ambitious research programme will produce several high-quality publications which will benefit the academic career prospects of ESRs. As recommended by the LERU Good Practice Elements in Doctoral Training[29], TRACT ESRs will establish research networks beyond their own discipline, essential for a future research career which is unlikely to remain limited to one narrow domain. They will benefit from the opportunity to develop an international profile at an early stage in their career through secondments, attendance at conferences, and network-wide training and meetings. The extensive training programme described in Section 1.2 includes training in proposal writing, teaching experience, and access to leading academic researchers, all of which will benefit their academic career prospects.

Exposure to leading research and technologies: ESRs recruited to the programme will work in a stimulating research and training environment with access to state-of-the-art infrastructure and facilities under the guidance of highly-experienced supervisors. Through secondments and participation in project-wide meetings and training events, TRACT ESRs will gain a wider exposure than researchers involved in traditional PhD programmes. This exposure will open new career perspectives beyond those related to their specific discipline, and equip them with the skills to enter careers that span sectors and disciplines. This will positively impact their career prospects in industry (SME/BIOTECH/PHARMA).

Innovation training: The Europe 2020 Flagship Initiative – 'Agenda for new skills and jobs'[30] emphasises the importance of promoting entrepreneurship, self-employment and innovation. ESRs trained through the TRACT programme will be introduced at an early stage to the concepts of creativity and entrepreneurship and how their discoveries can be translated to the commercial setting. A unique aspect of the TRACT programme is inclusion of training dedicated to innovation and entrepreneurship through the 'Innovation Academy'. This training will enable TRACT ESRs to pursue innovation through their research during the project but will also equip them with the requisite skills to pursue fresh ideas and new ventures in future positions. The formal nature of this training will enhance the attractiveness of TRACT graduates to future employers.

Career planning: ESRs in TRACT will have the opportunity to explore academic and non-academic careers, in line with the LERU Good Practice Elements in Doctoral Training. The TRACT programme includes both informal and formal supports for career planning. Unlike researchers engaged in more traditional PhD programmes, TRACT ESRs will receive support and input from both academics and non-academics through interactions with their own Support Team and with others across the consortium at project meetings. Participation in dedicated career workshops will also be required, with opportunities to develop essential complementary skills, such as networking, CV preparation and interview skills.

Mobility: Mobility is recognised as a key factor in research career progression. According to the EU Commission's Researchers' Report 2014[31] only 15% of researchers who currently work in the EU are 'mobile', with men significantly more likely to be internationally mobile than women. In line with the programme requirements, all ESRs will be required to undertake transnational mobility at recruitment. All ESRs will also participate in secondments in different countries from their host institution. Thus, TRACT ESRs will be exposed to new and different research and industrial cultures, so that they can experience firsthand the potential benefits of mobility and learn valuable skills for adapting to new working environments. They will also gain experience in managing the practical aspects of mobility, such as dealing with immigration requirements and moving country, in a supported environment. In these ways, TRACT will prepare ESRs to pursue a wider range of future career opportunities across Europe.

[29] (http://www.leru.org/files/publications/LERU_AP_15_Good_practice_elements_in_doctoral_training_2014.pdf)

[30] http://ec.europa.eu/social/main.jsp?catId=738&langId=en&pubId=626&type=2&furtherPubs=yes

31 http://ec.europa.eu/euraxess/index/cfm/services/researchPolicies

2.2 Contribution to structuring doctoral / early-stage research training at the European level and to strengthening European innovation capacity

2.2.1 Structuring training across Europe

The TRACT programme has been designed with close reference to the EU Principles for Innovative Doctoral Training[32] and it is expected that the programme will contribute to the mainstreaming of a multidisciplinary, intersectoral, structured approach to doctoral training in the TRACT host institutions and beyond. TRACT will provide evidence of the benefit of a multidisciplinary, intersectoral approach to PhD training to support changes in curriculum in the participating beneficiaries. TRACT will also demonstrate that formal links between academic and industry partners in the design of multidisciplinary structured doctoral programmes at a European level are an invaluable resource in the training of future ESRs. A number of PIs in the academic beneficiaries are already responsible for doctoral curriculum design. For example, Prof Zisterer was the Co-ordinator of the cancer stream of the very successful PRTLI structured PhD programme 'Molecular and Cellular Mechanisms underlying inflammatory processes' in TCD (2011-2015). Prof. Bagan (UVEG) is Co-ordinator of the structured doctoral programme in Dentistry and is Director of the School of Doctoral Programmes for the entire University.
The consortium also plans to interact with current and future related ITNs and research actions funded by the Commission, as described below (section 2.3.2).

2.2.2 Strengthening European innovation capacity

TRACT will strengthen European innovation capacity specifically in terms of contributions to European capabilities for cancer diagnostics and therapeutics for OOC. **Patentable and commercially exploitable discoveries relevant to OOC are expected to arise from the project**, including new diagnostic kits (swab-based genotyping) for diagnosis and therapy monitoring, and novel therapeutics. Despite efforts to screen for and pre-operatively select OAC patients for potentially curative surgery, the five-year survival rate in early stage disease is only 25-35%. The incidence of OAC in men has also risen 50% in the last 25 years[33]. This is due to late diagnosis of disease and resistance to chemotherapy. In order to identify novel therapeutic agents and improve outcomes for OOC patients, there is an urgent need to discover biomarkers for early detection of the disease and to better understand the molecular basis of metabolic transformation and drug resistance in OOC. The ambitious goal set by the 'Commission Communication on Action Against Cancer: European Partnership' is to reduce cancer incidence by 15% by 2020[34]. TRACT will contribute to this goal by early diagnosis and improved therapy of OOC. **Therapeutic benefits from the research programme are promising since a number of molecular drug targets and potential biomarkers have already been identified by pilot experiments** (see section 1.1.4).
There will also be more general impacts in terms of training researchers to deliver innovation in basic and applied research and bringing together European academics and industrialists. TRACT will contribute to delivering on the commitments of the Europe 2020 Flagship Initiative - Innovation Union,[35] in particular by **promoting excellence in education and skills development** through the proposed doctoral training programme. It will contribute to establishing Europe as a world-class science performer by generating a talent pool of internationally mobile researchers in the field of cancer research, an area of enormous significance to Europe, both societally and economically. The highly-talented cohort of researchers with international and intersectoral experience will greatly enhance the capacity of Europe to address the enormous challenge of cancer diagnosis and therapy. TRACT will also contribute to **removing the obstacles to innovation by addressing the skills shortage and the "knowledge gap" between academic researchers and the commercial world.** The project will contribute to a framework to deliver on the commitment to revolutionise how the public and private sectors work together by promoting the flow of researchers and expertise between the sectors.
Through the project, existing links between academia and industry will be strengthened and new links forged. This will not only open up broader career paths for the ESRs, but will also **drive more rapid, more effective translation of research findings into products** that will enhance cancer diagnosis and management, and will **deliver growth in revenue and employment** for European SMEs in the life sciences.
TRACT has the capacity to progress innovative multiplex companion diagnostics, with the inclusion of OOC genetic signatures, to the market. For example, partner organisation Almac has developed a microarray-based gene signature test for stage II colon cancer recurrence which was launched on the US market by Helomics

32 http://ec.europa.eu/euraxess/pdf/research_policies/Principles_for_Innovative_Doctoral_Training.pdf
33 http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oesophagus/mortality/#source1
34 http://ec.europa.eu/health/major_chronic_diseases/diseases/cancer/index_en.htm
35 http://ec.europa.eu/research/innovation-union/index_en.cfm?pg=action-points

Therapeutics Inc.® as GeneFX colon and a number of additional tests for breast, ovarian and prostate cancer are in Almac's development pipeline.

2.2.3 Contribution of the non-academic sector to the doctoral/research training

Non-academic partners will provide **state of the art training in drug design, biomarker discovery, exosome analysis, metabolism and therapeutics**. To achieve the ambitious objectives, all the ESRs will be seconded to SME/industry companies relevant to their chosen project across Europe for minimum periods of 3 months for intensive training in advanced technologies and research areas central to the TRACT theme. The TRACT SME/industry partners have been specifically identified as leaders in their field in terms of both technology and its application to cancer research and their involvement is essential for a full and integrated training program for the ESRs. TRACT will also **provide very useful networks of contacts to the researchers employed on the network grant for their future careers**. The specific capabilities of each SME/industry partner are incorporated into the programme overview. A potential impact of the close collaboration between the academic and non-academic partners may be the development of joint PhD programmes in future and also the exchange of other researchers between the sectors.

2.3 Quality of the proposed measures to exploit and disseminate the project results

2.3.1 Dissemination of the research results

Dissemination of research results from the project will take place via a number of channels.

Publications/presentations: Project results will be published in relevant peer-reviewed journals, such as Cancer Research and the British Journal of Cancer, and presented at relevant scientific conferences, such as the European Association of Cancer Research bi-annual meeting, oncology-specific conferences (such as ASCO or ESMO) or speciality conferences relating to OOC, 'omics and diagnostic assay technology. Material presented and published will adhere to the IP process established for the project to ensure exploitable outputs are protected in advance of dissemination.

Open Science: The TRACT consortium are supportive of the Horizon 2020 strategic priority of Open Science. To maximise research impact and to help promote diversity in science across the EU, we will pursue the 'green' route to open access through self-archiving (such as the TARA repository in TCD) and publication in open-access peer-reviewed journals, wherever possible.

Other projects: TRACT will engage with other related projects, such as Project Cyclon, a Marie Curie ITN, which is working on the development of a sugar-based anti-cancer drugs, and the Marie Curie ITN "Cancer Diagnostics: Parallel Sensing of Prostate Cancer Biomarkers" (PROSENSE) and the FP-7-ICT project "Virtual Physiological Human based predictive model for oral cancer reoccurrence in the clinical practise" (OraMod). The consortium will also approach newly funded projects over the TRACT lifetime. A related projects page will be created on the website. Other anticipated engagements include sharing the e-newsletter and invitations to project events.

2.3.2 Exploitation of results and intellectual property

It is expected that TRACT will **identify 1) novel biomarkers for diagnosing OCC and monitoring therapeutic response and 2) develop novel chemical and biological therapeutics**. Project partners intend to use these outputs to train ESRs in intellectual property management and to pursue commercial opportunities. For example, TRACT will develop a saliva-based diagnostic kit for early detection of dysplasia in OSCC suspect patients, which would be of commercial interest to clinical laboratories globally and could be developed by Almac as discussed in Section 2.2.2. **Therapeutic benefits from the research programme are promising since potential molecular drug targets and biomarkers have already been identified by pilot studies.**

All academic TRACT beneficiaries have dedicated Technology Transfer Offices to help biomedical researchers realize the economic, societal and commercial impacts of their findings. Since each ESR project is linked to an industrial partner, this further provides a unique potential for the commercial development of the data and to enhance public-private sector collaboration. Outputs generated from this programme may be transferred for commercial development through our industrial partners or commercialised through new spin-out companies. The best commercialisation approach will be determined on a case-by-case basis. Transfer of IP may form the basis for developing and expanding projects, enhancing public-private sector collaborations and creating future jobs. Fostering stronger links between industry and research will not only open up broader career paths for TRACT ESRs, but will also drive more rapid, effective translation of research findings into products to enhance cancer diagnosis and management, and deliver growth in revenue and employment for European Life Science SMEs.

TRACT Marie Skłodowska-Curie ITN Exploitation Workshop: All ESRs will work together to organize a half-day Exploitation Workshop, held in conjunction with the Open Day for stakeholder engagement. Representatives from

pharmaceutical companies and patient advocacy groups will be invited to attend the workshop. ESRs will deliver lectures to inform relevant commercial entities on the advantages of public-private collaborations and on the advances that have been made in OOC research through the programme.

In addition to generating commercialisable research outputs, TRACT will **advance the strategic research goals of all the host academic institutes**. For example, a major research priority in CCRCB in QUB is 'Biomarker discovery and validation that informs how patients are treated or predicts tumour sensitivity to therapeutic targets'. In addition, one of the 2014-2019 TCD strategic research goals is 'to focus on interdisciplinary research', such as that planned for TRACT. Furthermore 'Cancer' is a major research theme of TCD. TRACT, through its research outputs, will enhance the global reputation of the respective academic institutes as locations for knowledge creation.

2.4 Quality of the proposed measures to communicate the project activities to different target audiences

Communication and public engagement strategy of the project: This has been developed with a number of key audiences in mind, including cancer patients, future PhD candidates and the general public. Involvement of the ESRs in communication and public engagement is central to the strategy - all ESRs will be involved in a minimum of two outreach activities per year. The aim will be to raise public awareness of cancer research and more generally increase public engagement with and understanding of science, as well as developing ESRs' understanding of public interest and science-related priorities. The impact of the outreach activities for both the public and ESRs will be assessed by a number of methods, including questionnaires and interviews.

Web-based outreach activities: A project website will be created as the central online dissemination tool. ESRs will regularly contribute content to the site, as well as contribute to a six-monthly e-newsletter aimed at informing the general public about OOC and about the project findings in particular. A Wikipedia page will also be created and maintained by the ESRs. Social media accounts (Facebook, Twitter) will be created and maintained by ESRs and each will contribute to regular blog posts giving an update on their research and training activities. The impact of these activities in raising awareness will be measured by numbers of hits to the website, and reach of the social media accounts. To measure the impact on increased engagement metrics will include numbers of retweets, comments and replies.

Media: Networks within the Communications Offices of all partners will be leveraged to establish a project presence in the popular media. For example, a press release will be issued at the project kick-off. Where publications are likely to attract wider public interest, authors will work closely with Communications Offices to maximise coverage in the popular media. Many TRACT investigators already have a proven track record in public engagement. For example, Prof. O'Neill (Opsona) currently has a weekly slot with a national Irish broadcaster. This impact will be measured by numbers of media articles and radio/television spots.

Outreach to OCC patient groups: The TRACT research programme is of particular relevance to OCC sufferers, their families and friends. Each year, QUB hosts an information day for members of the Oesophageal Patient Association and the Oesophageal Cancer Fund. Dr. Turkington (QUB) will chair an outreach session at this information day (M18), where all ESRs will present their research to a lay audience. This session will educate the public about the existence of European projects to improve OOC diagnosis and treatment, while also offering ESRs with an opportunity to engage with those who may benefit from their work, potentially inspiring a deeper interest in the field of cancer research. In addition, ESRs based at QUB will have the opportunity to engage with the public through the Northern Ireland Cancer Consumer Research Forum - ESRs will give lab tours and talks to members of the Forum in order to promote greater public understanding and involvement in cancer research.

Outreach to secondary school students*:* Inspiring the next-generation of PhD candidates requires early exposure of cutting-edge science. All the host beneficiaries will be involved in outreach programmes to secondary school students. For example, currently the School of Biochemistry & Immunology, TCD, run a 'transition year' programme where secondary school students (15-16 years old) spend a week in laboratories within TCD. Each secondary school student spends time participating in scientific activities and group activities with talks, quizzes and visits to other scientifically relevant sites on the TCD campus. Similar schemes will be set up by other beneficiaries. Impact of these outreach activities will be measured through questionnaires distributed to students before and after the events.

Science Gallery and related global network**:** TRACT is fortunate to have direct access to the world-leading Science Gallery (www.sciencegallery.com) based in TCD. Since 2008, the Science Gallery has attracted more than 1.9 million visitors to 34 exhibitions, ranging in theme from contagion to the future of fashion. It has recently

partnered with Google to establish a global network of science galleries, modelled on the Science Gallery approach to engaging young people in science. TRACT will engage in debates and information events run by the Science Gallery. Science Gallery have considerable experience in measuring impact of science communication activities.

EU Researchers' Nights and other local events: Where possible, ESRs will participate in on-going initiatives run by the beneficiaries. For example, ESRs will participate in EU Researchers' Nights, such as those hosted by TCD and UNISI. Live links between Siena, Dublin and the other beneficiaries will allow all ESRs to participate in both Nights. TCD led by the Trinity Biomedical Sciences Institute, was awarded funding to host an 'EU Researchers' Night' event in 2014 and 2015. The event had over 7,000 attendees each year and features a wide range of interactive and hands-on activities for the general public that aim to challenge perceptions held by the general public about researchers, to promote research as an exciting career option, to demonstrate creativity and innovation in research across all disciplines and to show that researchers are dynamic contributors to society. It is anticipated that the event will continue to be held annually. Marie-Skłodowska Curie Fellows are central to the organisation of this event, and ESRs recruited to TRACT at TCD will organise events, present their research and have representation on the Steering Committee for future EU Researchers' Nights. Similarly, UNISI is partner in the Researchers' Night "Scientists are Humans: Interactive Night of Entertainment - SHINE!", and every year in September, UNISI organizes a number of initiatives dedicated to young researchers (http://www.unisi.it/shine), in which ESRs based at UNISI will participate. Impact assessment through qualitative and quantitative measures is a key deliverable of Researchers' Nights and TRACT ESRs will contribute to this.

***TRACT Marie Sklodowska-Curie ITN Open Day*:** All ESRs will organise and participate in the Open Day (M36), helping them develop project management and event organisation skills. Attendees will include the general public and other interested lay audiences, such as patient group representatives. The event will include presentations from the ESRs on their research results, as well as open question sessions. The aim of the Open Day is to communicate the project findings and give ESRs an opportunity to develop communication skills. Impact will be measured through numbers of attendees and quality of discussions.

3. Quality and Efficiency of the Implementation

3.1 Coherence and effectiveness of the work plan

Table 3.1 a: Fellows Individual Research Projects

ESR1	**Host institution (UVEG)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(2.1,2.5)***
Project Title: Inflammatory response elements and glycan profiles as salivary biomarkers for the early diagnosis of oral cancer (WP2; Task 2.1))					
Objectives: Complete a research training programme in: • Translational clinical research • Molecular and biochemical techniques for the study of inflammatory activation and regulation • Molecular and biochemical techniques (e.g. LC-MS) for the study glycan profiles					
Expected Results: • Identification of significant differences in salivary and serum glycan profiles, inflammatory markers, homeostatic chemokines amongst patients with potentially malignant disorders (group 1), with OSCC (group 2) and age/gender matched controls (group 3). • Identification of differences in salivary and serum glycan profiles, inflammatory markers, homeostatic chemokines between OSCC patients in early stages (stage I and II) and those with advanced stages (stage III and IV) and examination of any gender differences					
Planned secondment(s): NIBRT, (Rudd, 3 months from M14) - glycan analysis.					

ESR2	**Host institution (QUB)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(2.3,2.4,2.5)***
Project Title: Identification of Novel Molecular Biomarkers Predictive of Benefit to Neo-adjuvant Chemotherapy in Oesophageal Adenocarcinoma (WP2; Task 2.2)					
Objectives: Complete a research training programme in: • Development of integromic biomarkers capable of predicting response to chemotherapy in early stage OAC • Analysis of high-dimensional whole genome sequencing, methylation and microarray data					

Expected Results:
- Identification of molecular signatures predictive of response to chemotherapy in OAC
- Retrospective validation of resultant predictive classifiers
- Discovery of the biology underpinning the predictive classifier

Planned secondment(s): Almac Diagnostics, (Davison, 3 months from M9)- biomarker development. TCD, (Creagh, 5 months from M25)- functional analysis of the underlying biology of predictive classifiers.

ESR3	**Host institution (UVEG)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(2.2,2.5)***

Project Title: Modulation of salivary inflammatory markers in patients undergoing radiotherapy for OSCC. A potential tool for identifying toxicity to irradiation (WP2; Task 2.3)

Objectives: Complete a research training programme in:
- Translational clinical research
- Molecular and biochemical techniques for the study of inflammatory activation and regulation

Expected Results:
- Correlation of salivary inflammatory marker levels with tumour control in patients undergoing radiotherapy
- Examination of saliva as a putative prognostic test as a predictor of a patient's response to radiotherapy
- Potential for IP and bedside test development

Planned secondment(s): IME-SP, (Windshügel, 3 months from M13) - biomarker discovery, inflammatory cytokine profile from patient samples utilising the MesoScale Discovery platform.

ESR4	**Host institution (QUB)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(3.5,3.7)***

- Project Title: A Pathways-based Approach to Identify Determinants of Drug Resistance in Oesophageal Adenocarcinoma (OAC). (WP3; Task 3.1)

Objectives: Complete a research training programme in:
- Combined RNA-seq and microarray analysis of differentially expressed/ frequently mutated genes in responders/non-responders
- Pathways-based analysis using Gene Set Enrichment Analysis and Gene Ontology analysis to determine pathways governing drug resistance. Preliminary data analysis has identified the MAPK and glycolytic pathways as potential targetable pathways
- Construction of siRNA screens of candidate genes
- Validation of potential novel drug targets in suitable panel of in vitro cell lines, primary tumour-derived cell lines and patient-derived xenograft models

Expected Results:
- Discovery of the molecular pathways regulating drug resistance in OAC
- Validation of drug targets to develop strategies for overcoming resistance to chemotherapy
- Discovery of the molecular pathways regulating drug resistance in OAC

Planned secondment(s): IME-SP (Windshügel, 3 months from M9) - industry experience in target selection and drug development. Almac Diagnostics (Davison, 3 months from M15) - ontological analysis of microarray datasets. TCD (Zisterer, 5 months from M23) - biological functional analysis of drug resistance in OAC.

ESR5	**Host institution (TCD)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(3.1,3.7)***

Project Title: Inflammatory caspase expression during oesophageal carcinoma. (WP3; Task 3.2)

Objectives: Complete a research training programme in:
- Immunohistochemical (IHC)-based profiling and analysis of OAC patient biopsies
- Molecular and biochemical techniques for the study of inflammasome activity and inflammation
- Screen novel inflammatory modulators/caspase inhibitors in co-culture and animal models of OOC

Expected Results:
- Establish the expression profiles of human inflammatory caspase-1, -4 and -5 during OAC tumour progression/resistance
- Examine the influence of inflammatory caspase expression on inflammatory, growth and angiogenic markers in a co-culture model system
- Target inflammatory caspase expression using novel anti-inflammatory modulators and caspase inhibitors, in co-culture and animal models of OOC.

Planned secondment(s): QUB (Turkington, 4 months from M13) - IHC analysis of inflammatory caspases in OAC (responder/non-responder) biopsies. Opsona Therapeutics (O'Neill, 3 months from M30) - screen efficacy of novel anti-inflammatory drugs in OOC cell culture and mouse models.

ESR6	**Host institution (UNISI)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(3.2,3.4,3.6,3.7)***
Project Title: Novel Mcl-1 inhibitors for the treatment of OSCC (WP3; Task 3.3)					
Objectives: Complete a research training programme in: • Computational chemistry and rational drug design • Organic synthesis of novel chemical entities and scale up procedures • Screening of compounds in OSCC models • Profiling of exosomes/EVs in OSCC models prior and after treatment with Mcl-1 inhibitors					
Expected Results: • Synthesis of novel Mcl-1 inhibitor(s) • Identify lead compound which induces cell death in OSCC • Identification of EV associated molecules as stratification markers for targeted therapies and/or surrogate markers for therapy monitoring					
Planned secondment(s): TCD (Zisterer, 3 months from M28) - testing of drugs on OSCC model; Exosomics (Chiesi, 3 months from M31)- extraction of exosomes from OSCC cells and miRNA/DNA/protein content evaluation					

ESR7	**Host institution (TCD)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration *(36 months)***	**Deliverables *(3.3,3.7)***
Project Title: HAMLET derivatives as a pre-operative therapy in oesophageal cancer (WP3; Task 3.4)					
Objectives: Complete a research training programme in: • Chemical design and synthesis • NMR (nuclear magnetic resonance) metabolite analysis • Analysis of metabolic changes by respirometry • CRISPR and next generation sequencing					
Expected Results: • Development of highly effective tumouricidal HAMLET derivatives. Identification of their mode of action in oesophageal cell lines by genome scale CRISPR-Cas9 knockout					
Planned secondment(s): UNISI (Campiani, 5 months from M7) - chemical design and synthesis and Oroboros (Gnaiger, 3 months from M21) - analysis of metabolic changes.					

ESR8	**Host institution (UNISI)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(3.2,3.4,3.6,3.7)***
Project Title: Development of novel autophagy modulators to improve sensitivity of OSCC to chemotherapy (WP3; Task 3.5)					
Objectives: Complete a research training programme in: • Bioinformatics and computational drug design • Synthesis of novel compounds to specifically inhibit autophagy processes • Biochemical techniques for the study of mechanisms of cell death • Quantitative and qualitative analysis of OSCC released EVs for monitoring of autophagy modulating therapy					
Expected Results: • Development of highly effective novel autophagy protein modulators for OSCC • Identify their efficacy in OSCC cell lines • Identification of surrogate markers for novel compound screening in OSCC cell line model					
Planned secondment(s): TCD (Zisterer, 3 months from M25) - testing of drugs on OSCC cell lines; Exosomics (Chiesi, 3 months from M28)- extraction of exosomes from OSCC lines and miRNA/protein content evaluation					

ESR9	**Host institution (TCD)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration (36 months)**	**Deliverables *(3.6,3.7)***
Project Title: Pre-clinical evaluation of targeting autophagy for the treatment of OSCC (WP3; Task 3.6)					

Objectives: Complete a research training programme in: • Molecular, biochemical and genetic techniques, imaging techniques relevant to autophagy/apoptosis • Analysis of expression of autophagy proteins as potential biomarkers in OSCC patient samples • Testing pharmacological and genetic inhibition of autophagy as a chemosensitising strategy for OSCC.
Expected Results: • Identify clinically relevant biomarkers of OSCC disease that can be used for earlier disease detection, • Determine whether combining existing OSCC chemotherapy strategy with autophagy inhibition represents a better treatment strategy that could be translated into benefit for OSCC patients.
Planned secondment(s): UVEG (Bagan, 3 months from M13) - immunohistochemistry and PCR analysis of OSCC patient samples. Andor (Hanrahan, 3 months from M25) - live cell imaging of autophagy using advanced fluorescent probes.

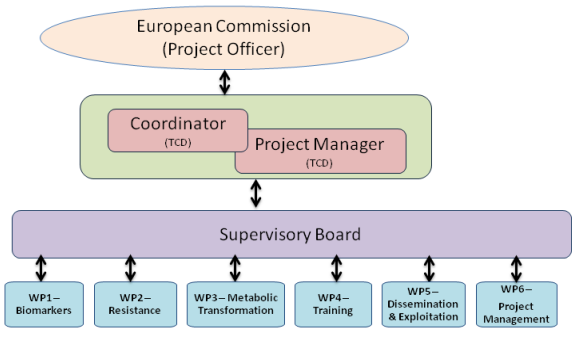
ESR10	**Host institution (Oroboros)**	**PhD enrolment Y (Univ. of Innsbruck)**	**Start date (Month 6)**	**Duration *(36 months)***	**Deliverables *(4.1,4.3,4.4)***
Project Title: Metabolic profiles in normal, dysplastic and cancerous oral cells (WP4; Task 4.1)					
Objectives: Complete a research training programme in: • High-resolution Respirometry to measure real-time bioenergetics and metabolism • NMR metabolomics					
Expected Results: • Comparison of oxygen consumption, extracellular acidity and metabolic flux in different cell types under normoxic and hypoxic conditions and correlate with chemotherapy sensitivity • Identify differential novel drug targets in the cancer cells					
Planned secondment(s): TCD (Porter, 9 months from M13) - measure metabolic flux through (a) glycolysis, (b) pentose phosphate pathway and (c) glutaminolysis using 2H/13C NMR.					

ESR11	**Host institution (TCD)**	**PhD enrolment Y**	**Start date (Month 6)**	**Duration *(36 months)***	**Deliverables *(4.2,4.3,4.4)***
Project Title: Mitochondrial morphology linked to metabolic differences in normal, dysplastic and cancerous oral cells (WP4; Task 4.2)					
Objectives: Complete a research training programme in: • High-resolution respirometry to measure real-time bioenergetics and metabolism • Confocal microscopy to observed mitochondrial fission/fusion/mitophagy • Immunoblotting & quantitative RT-PCR					
Expected Results: • Correlate bioenergetics status and cisplatin sensitivity of the cells over a range of glucose/galactose ratios to mitochondrial morphology • Identify the functional proteins involved in mitochondrial dynamics.					
Planned secondment(s): Oroboros (Gnaiger, 6 months from M10) - measure real-time cellular bioenergetics, metabolism					

3.2 Appropriateness of the management structure and procedures

3.2.1 Network Organisation and Management Structure

Management of the project will depend on robust management principles that incorporate strong leadership from the project **Coordinator** Dr. Zisterer. Dr. Zisterer has over ten years experience in participating in large multi-centre projects. She was recently the Coordinator of the cancer stream of the PRTLI structured PhD programme (2011–2015) entitled 'Molecular and Cellular Mechanisms underlying inflammatory processes,' which included 4 partner Universities with a budget of 7.2 million euro. Trinity Research & Innovation and the Financial Service Division at TCD will provide overall legal and financial management of the project. Both Offices have considerable experience in large multinational and European projects - TCD currently successfully coordinates in excess of 20 FP7 projects and has been involved in over 200 FP7 projects. A dedicated **Project Manager** will be hired to oversee day-to-day operations of the project. Specifically, the team at TCD will be responsible for the overall management of the project, communication between all partners and the Commission, distribution of funds, collation of annual reports and financial statements for the Commission, overseeing recruitment and risk management. TCD will also provide a virtual communication centre to advance the mutual exchange of knowledge through



internet forums, a wiki, communication/conferencing tools and websites.

Financial management strategy: As Coordinator, TCD will be responsible for dispersal of funding to all beneficiaries and overall financial management of the project, including submission of cost claims. Each beneficiary will adhere to their local financial management practices and requirements of the H2020 programme.
Scientific misconduct: Research integrity is a priority of all TRACT partners. ESRs will be briefed on the importance of ethics and integrity in research during induction to their recruiting institution, and bioethical research will be discussed at the Kick-off meeting (M6). ESRs and Support Teams will report suspected misconduct of any project participant to the SB who will ensure relevant local procedures are followed.
WP leaders have been assigned to each WP - each WP leader will be responsible for ensuring all activities are delivered according to plan. The Coordinator and Project Manager will hold monthly virtual meetings with each WP leader, organising cross-WP virtual meetings as needed to promote synergies between the research themes.

3.2.2 Supervisory Board

A Supervisory Board (SB) will be established to support the Coordinator and Project Manager in overseeing the research, training and dissemination activities of the project. The SB will be composed of **representatives from all beneficiaries and partner organisations** (Chair: Zisterer (TCD), Members: Bagan (UVEG), Campiani (UNISI), Turkington(QUB), Gnaiger (Oroboros), Hanrahan (Andor), Davison (Almac Diagnostics), Rudd (NIBRT), Liversage (Seahorse), O'Neill (Opsona), Windshügel (IME-SP), Chiesi (Exosomics)). An **ESR representative** will also be nominated to join the SB at the Kick-off meeting. An **External Advisor,** Prof. Gavin Davey (TCD, Coordinator of the FP7-funded ITN TINTIN), will also sit on the SB. The SB will strive for consensus in decision-making - in the event consensus cannot be reached, the Coordinator will hold the deciding vote.
Importantly, the SB will be involved in monitoring ESR progress, through initial approval of all PDPs (M7) and on-going review of progress with the designated Support Teams through six-monthly reports. The SB will monitor:

- **Training planning/content** - by ensuring the PDP for each ESR includes challenging, yet achievable, training goals with a balance between scientific/technological and complementary skills training; by ensuring that emerging needs of both academic and non-academic sectors are being addressed by the project and amending the training, as required, and that the project is maximizing potential synergies,
- **ESR progress** - through assessment of ESR research presentations at annual meetings and six-monthly progress reports summarising research, training and dissemination activities against PDPs/research plans,
- **Training quality** - by ensuring consistent quality of training across all sites, reviewing training agenda/content in advance of training events and obtaining feedback after training events to support future improvements,

Conflict resolution - The SB will also act to resolve conflicts between ESRs and their ESR Support Team, individual ESRs or PIs should the need arise. The SB will offer robust 'Adaptable Conflict Resolution' pathways, such as facilitated dialogue and shuttle negotiation. The ESR representative on the SB will not be involved in any conflict resolution or progress reviews of their peers.

3.2.3 Recruitment strategy

Recruitment of suitably trained, motivated researchers will be central to success of the project and will be carried out as per the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers.[36] The academic institutions TCD, UNISI, QUB and Medical University of Innsbruck (where ESR10 will be registered) have officially endorsed the Charter and Code. As further evidence of the consortium commitment to the principles, partner QUB has been granted permission to use the "HR Excellence in Research" logo.
A **centralised recruitment strategy** will be implemented. The recruitment strategy will be aligned with the Charter and Code and consistent with local practices, and be developed as a priority in M1 by the SB. The strategy will also be informed by the Erasmus Mundus Handbook of Excellence – Doctoral Programmes[37]. Recruitment will begin as soon as possible to capture the attention of the best students. A professional project website and social media accounts will be developed as a priority. Marketing of the programme is critical to ensure that excellent international doctoral candidates are motivated to apply for TRACT. To ensure openness and transparency and maximum reach, positions will be widely advertised on accessible websites and journals (www.findaphd.com, www.researchgate.com, New Scientist, Nature, Science) and the pan-European Researcher's Mobility Portal.[38]

36 http://ec.europa.eu/euraxess/index.cfm/rights/whatIsAResearcher
37 http://eacea.ec.europa.eu/erasmus_mundus/tools/documents/repository/handbook_of_excellence_2012_doctoral_en.pdf
38 http://ec.europa.eu/euraxess/index.cfm/jobs/index

The call for applications will clearly describe the minimum requirements (BSc/Master or equivalent in science and meet the mobility and selection criteria of the ITN scheme) , the selection criteria (including relevance of research training and experience and level/quality of degrees awarded), the information that applicants must provide (CV, completed application form and at least two letters of reference from professionals involved in their previous training) and a description of the working conditions and entitlements, including career development prospects. A selection committee will be established with inter-sectoral representation and gender balance. Shortlisted candidates will be interviewed either face to face or via Skype if required. Candidates will be scored according to the published selection criteria - a minimum threshold score will be agreed in the recruitment strategy. Fellowships will be offered to the first ranked candidates and, should they not accept, to the next ranked candidate meeting the threshold score. The closing date for applications will be the end of M2, with recruitment completed by M5.

Equal opportunity will apply to the recruitment process with no discrimination on the basis of gender, age, ethnic, national or social origin, religion or belief, sexual orientation, language, disability, political opinion, social or economic condition. As recommended by the Charter, this will not take precedence over quality and competence criteria. The Human Resources Offices in the recruiting beneficiaries will provide advice to the recruitment process on all aspects of local employment law. All ESRs will be employed on a full time contract by their host organisation (36 months) and be entitled to social security provision, including sickness, parental benefits, pension and unemployment benefits. International Student Offices at the host institutions and the SB, will support recruited researchers on mobility issues. Candidates will also be directed to national mobility portals, such as www.euraxess.ie, for practical support.

3.2.4 Progress Monitoring and Evaluation of Individual Projects

The PDPs developed by each ESR with their Support Team are at the core of training progress monitoring - the **PDPs will detail the training planned for each ESR and mechanisms for on-going assessment of progress**. PDPs will also include a detailed research plan, including deliverables and milestones, which will be used to monitor progress. As all ESRs will be enrolled in a PhD programme, progress against any local programme requirements will also be tracked by the Support Team and SB. For example, in TCD there is a requirement for all PhD students to submit a progress report 18 months into their degree. Students must also give a formal research talk followed by a viva voce examination by two independent examiners within TCD with experience in the field of research. A formal report with suggestions for future studies is then provided to the students and their supervisor(s).

Progress monitoring for all ESRs will be overseen by the ESR Support Team (see 1.3.2) on a regular basis. Each ESR will meet weekly with their Primary Supervisor when at the recruiting institution and the relevant Secondary Supervisor while on secondment. Monthly meetings will take place between ESR and their full Support Team (virtually or face-to-face) where they will be provided with informal feedback. The SB will also monitor progress (research, training, dissemination) on a six-monthly basis based on reports from each ESR and their Support Team. The SB will provide formal written feedback on progress after ESR presentations at the annual meetings.

3.2.5 Intellectual Property Rights (IPR)

IPR management will be detailed in a Consortium Agreement (CA) agreed and implemented by all partners before the project starts. The CA will specify the processes for management of IPR, including appropriate management of knowledge (protection of know-how, exclusion of background, access rights, etc.). The CA may set out specific rights and obligations of the partners, which may integrate or supplement, but which will under no circumstance be in conflict with those of the Grant Agreement. IPR disputes that cannot be resolved within the consortium shall be finally settled under the Rules of Arbitration of the International Chamber of Commerce by one or more arbitrators. The award of the arbitration will be final and binding upon the partners. The Technology Transfer Office (TTO) in each beneficiary will look after any potential IP generated in that beneficiary and will liaise with the TTO in other beneficiaries should joint IP arise.

Following the generation of potential IP, PIs will work with the relevant ESR to submit invention disclosure forms to the Technology Transfer Office in the relevant host institution and inform the Coordinator. From a **training perspective**, ESRs will be introduced to the issues and actions associated with quality assessment, early identification and protection of intellectual property from modules given at the Innovation Academy. From a **commercialisation perspective**, TRACT beneficiaries and partners have an exceptional track record in the successful patenting and commercial exploitation of research. TCD has produced more entrepreneurs than any other university in Europe over the last five years, according to The Universities Report by private equity and venture capital-focused research firm, PitchBook. TRACT Co-ordinator, Dr. Daniela Zisterer has two patents on novel anti-cancer drugs and Prof. Giuseppe Campiani has 15 patents on pro-apoptotic and anti-psychotic drugs in

collaboration with Sigma-Tau and Eurosearch/GSK. Prof. Richard Kennedy's group has extensive experience in developing microarray-based biomarkers having identified a 634-probe set prognostic signature in Stage II colon cancer and a 44 gene signature predictive of response to DNA-damaging chemotherapy by characterising DNA damage response-deficient primary breast tumours. Both of these biomarkers have been licensed to global biotech companies (one to Genomic health (US) for $9 million plus royalties) for validation and are scheduled to enter clinical usage shortly. ESRs in the programme will benefit from this experience, directly through their supervision arrangements and indirectly through project events, such as the project-wide meetings.

Training in IPR will be included in the PDPs for all ESRs. In addition, the IP policies and practices of each employer/host will be set forth in detail to each incoming ESR before any grant-supported work begins. ESRs will sign a non-disclosure agreement regarding all research activities, if specifically requested by the associated partners' institutions. ESRs will be expected to retain first author rights on publications of their research. ESRs working at private-sector partners will be advised of their legal rights to their results before commencing work.

3.2.6 Gender Aspects

The consortium recognises the advancement of gender equality: representation, progression and success for all as detailed in the Athena Swan charter (https://www.tcd.ie/diversity-inclusion/athena-swan/). QUB is the recipient of an Athena Swan award.

Decision-making: The SB will be responsible for overall decision making for the project. There will be an adequate gender balance on the SB, aiming to reach the Commission's target of 40% of the under-represented sex.

Recruitment: During recruitment of ESRs, an equal opportunity policy will be implemented. However, this will not take precedence over quality and competence criteria in line with the European Charter for Researchers and Code of Conduct for Recruitment. Shortlisting panels and interview committees will have adequate gender balance to ensure equal treatment of candidates. Project supervisors will promote gender balance in their research teams, through equal opportunity hiring, flexible working conditions and work-life balance initiatives wherever possible. For example, the host institutes will provide compulsory annual leave, flexible working hours and will foster an environment that encourages ESRs to engage in social/leisure/family activities.

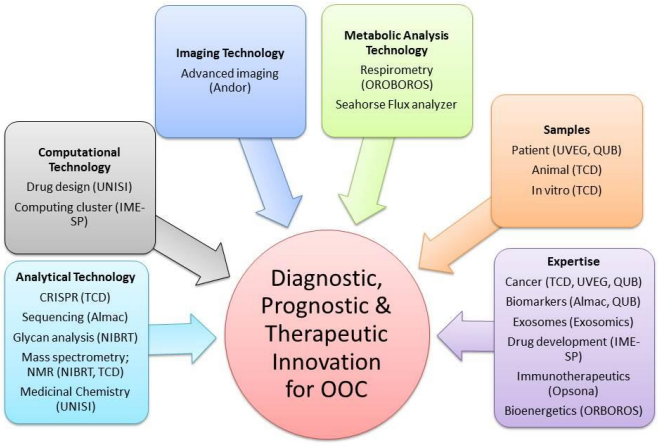
3.3 Appropriateness of the infrastructure of the participating organisations

There are 12 legal entities participating in the TRACT programme, each of which have the required infrastructure to support the main tasks attributed with their involvement in the programme, as summarised below.

Institution	*PhD programme*	*Innovation training*	*Science communication*	*Cell imaging/microscopy*	*Metabolic analysis*	*Drug discovery*	*Biomarker discovery*	*Biomarker development*	*Mito. respiration*	*Exosome isolation/analysis*	*Glycobiology analysis*	*Bioinformatics*	*Patient perspective*	*IP management*	*Project Management*
TCD	X	X	X	X	X									X	X
QUB	X	X	X										X	X	X
UNISI	X		X			X								X	X
UVEG	X		X				X	X						X	X
Oroboros	X		X						X					X	X
Andor				X										X	X
Opsona						X								X	X
ALMAC							X	X				X		X	X
NIBRT							X	X			X			X	X
IME-SP						X	X	X						X	X
Exosomics						X				X				X	X
Seahorse					X									X	X

3.4 Competences, experience and complementarity of the participating organisations and their commitment to the programme

3.4.1 Consortium Composition and Exploitation of Partners' Complementarities



Research expertise: Delivering diagnostic, prognostic and therapeutic innovation for OOC requires expertise in a number of research domains as summarised here diagramatically. **Access to samples:** The discovery work planned for the project relies on in vitro, in vivo and ex vivo samples, all of which will be provided from within the consortium - animal models (TCD) and patient samples (UVEG, QUB). **Access to technologies:** Our research innovation relies on information obtained from leading edge technologies, that are all available within the consortium including Seahorse Flux analyser (Seahorse), qPCR, array and next-generation sequencing platforms (Almac), in silico drug development (UNISI), advanced imaging (Andor), glycan assays (NIBRT), exosome purification and analysis (Exosomics), mass spectrometry (NIBRT, UNISI), biomarker assays (QUB), NMR (TCD), high throughput drug screening (IME-SP), computing cluster (IME-SP), high-resolution respirometry (OROBOROS), whole genome sequencing (QUB), CRISPR generated cancer models (TCD) & analytical chemistry assays (HPLC, etc.) (UNISI, NIBRT).

3.4.2 **Commitment of beneficiaries and partner organisations to the programme**

Beneficiary	**Research Activities**	**Training Activities**
TCD (IE)	Autophagy & Inflammation; autophagy as a target; pre-operative therapies; and metabolic analysis, of oral and oesophageal cancer patients and models (ESR 5, 7, 9, and 11)	Research Ethics; Tumour histology; Antibody technology; CRISPR generated cancer models; drug discovery; Whole body imaging in xenograft cancer models; Innovation academy and career development workshops (All ESRs)
QUB (UK)	Novel biomarkers and drug resistance pathways specific to OAC patients (ESR 2, 4)	Science communication; Computational biology; OOC patient outreach; Career development workshop; Introduction to OOC workshop (All ESRs)
UVEG (ES)	Inflammatory and glycan profiles as markers of oral cancer severity and patient responses (ESR 1, 3)	An introduction to OOC workshop; Biomarker Discovery workshop (All ESRs)
UNISI (IT)	Anti-apoptotic protein inhibitors, autophagy modulators as potential therapies (ESR 6, 8)	Drug Discovery and Medicinal Chemistry workshop (All ESRs)
OROBOROS (AT)	Metabolic profiles in normal, dysplastic and cancerous oral cells (ESR 10)	Training in mitochondrial and cellular respiratory physiology (All ESRs)
Partner	**Research Activities**	**Training Activities**
IME-SP (DE)	Gene profiling in OAC responder/non-responder groups and OSCC patient samples	Biomarker discovery – via multiplex analysis systems (ESR 3; ESR 4)
Almac Diagnostics (UK)	Analysis of potential biomarkers in molecular pathways differentially activated in OAC patients	Biomarker development (ESR 2; ESR 4)
Opsona Therapeutics (IE)	Testing immunomodulatory drugs in OOC cell culture & mouse models	Training in cancer immunology (ESR 5)
Exosomics(IT)	Exosome analysis from OSCC cell lines untreated/treated with Mcl1-inhibitors or autophagy inhibitors	Exosomes extraction/purification from cells and DNA/protein/miRNA analysis (ESR 6; ESR 8)
Andor (UK)	Live cell imaging of autophagy in OSCC models	High resolution confocal microscopy (ESR 9)
NIBRT (IE)	Analysis of serum/salivary glycan profiles in OSCC patient samples	Glycoanalytics (ESR 1)
Seahorse Biosciences (UK)	Metabolic analysis in normal, dysplastic and cancerous oral cells	Use of Metabolic Flux Analyzer (ESR 10 (OROBOROS); ESR 7, 11 (TCD))

4. Gantt Chart

	Months	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
	ESR 1														S	S	S																									T						A
	ESR 2									S	S	S														S	S	S	S	S												T						A
	ESR 3													S	S	S																										T						A
	ESR 4									S	S	S				S	S	S						S	S	S	S	S														T						A
	ESR 5													S	S	S	S														S	S	S								T						A
	ESR 6																												S	S	S	S	S	S							T						A
	ESR 7							S	S	S	S	S											S	S	S																	T						A
	ESR 8																									S	S	S	S	S	S											T						A
	ESR 9													S	S	S										S	S	S														T						A
	ESR 10													S	S	S	S	S	S	S	S	S																				T						A
	ESR 11										S	S	S	S	S	S																										T						A
Training	Scientific Training																																																
	Complementary Skills Training																																																
	Conference																C												C													C						
	Visiting Scientist						V												V											V														V				
M'ment																																																	
	Project Meetings						K												1												2														3			E
Dissem. / Public e'ment	Dissemn.																																									P	P	P			
	Public engagement										RN			SS					PT				RN			SS					PT				RN	OD		SS									

S = Secondment; T = PhD thesis submission; A = Award of PhD; K = Kick-off meeting; E = End of project; C = annual cancer conference; P = Publications submitted/patents filed; RN = Researchers' Night; PT = OCC Patient Info Day; SS = school student intern programmes; OD = Open Day

5. Ethics Issues

Relevant national legal and ethical requirements

Patient biopsy samples are required for the research projects described in WP 2-4 and it will be necessary to distribute biopsy samples, or derivatives thereof, to TRACT partners across European borders. Regulations covering the use of human tissue are set out in **The European Union Tissue and Cells Directives** (EUTCD). The EUTCD is made up of three Directives, the parent Directive (**2004/23/EC**), which provides the framework legislation and two technical directives (**2006/17/EC and 2006/86/EC**), which provide the detailed requirements of the EUTCD. Directive 2004/23/EC sets the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. TRACT beneficiaries and partners will ensure that all activities, imports and exports of human tissues.

Each of the ESR projects which requires the use of human samples will apply to local Ethics committees for approval in advance of applying to the respective national competent authorities (Office for Research Ethics Committees Northern Ireland, UK; Irish Medicines Board, Ireland; Organización Nacional de Trasplantes, Spain) in order to obtain individual authorisation.

Both local statutory instruments and EU Directives stipulate that for human participants involved in research, the autonomy of the potential research participant must be respected by providing, in clear and accessible format, the maximum information on the implications of participation in a project and allowing independent and informed decision-making on whether to participate. The information will include written details of risks and benefits in participating, and a guarantee of confidentiality. Where possible this will be ensured through implementation of a controlled scheme for participant anonymisation. It is expected that participants will sign a consent form to agree to take part in the research and in all cases the participants will be made aware of their right to withdraw from the research without penalty at any time.

Patients from the following groups will be excluded from the studies, children under 18 years of age, adults with learning disabilities, adults with communication difficulties, adults who are unconscious or very severely ill, adults who have a terminal illness, adults with mental illness, adults suffering from dementia, prisoners, young offenders, pregnant women and those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, students.

The study of molecular biomarkers and mechanisms of drug resistance in early stage oesophageal adenocarcinoma (OAC) will require access to retrospective OAC biopsies and resection specimens, as well as the prospective collection of OAC tissue suitable for genomic analysis. We have developed a database of OAC patients treated with neo-adjuvant chemotherapy followed by surgical resection in Northern Ireland from 2004-2014. Access to samples within the Belfast Trust is governed by the Northern Ireland Biobank (NIB13/0032) and ethical approval for the other three Health Trusts within Northern Ireland (Northern, Western and Southern Trusts) has already been granted by the Office of Research Ethics Committees of Northern Ireland (ORECNI; ref 13/NI/0149). National Health Service Research and Development approval has been obtained from all four health trusts in Northern Ireland for participation in the project and provision of biopsy and resection materials.

Prospective tissue collection is co-ordinated by the Northern Ireland Biobank (NIB) who have ethical approval for the collection and storage of tissue, blood and bodily fluids for use in approved research studies. Fresh frozen pre-treatment endoscopic biopsies and resection tissue have been collected prospectively since February 2015 and are available for the investigation of molecular markers and targets as well as the generation of patient-derived cell line models. Patients with potentially resectable oesophageal or gastro-oesophageal junction tumours are identified at the regional Upper Gastrointestinal Cancer Multidisciplinary meeting and initial contact is made by a nurse specialist at the surgical assessment clinic and a NIB patient information sheet provided. Informed consent is obtained (NIB consent form) after at least 24 hours and fresh frozen and formalin fixed biopsies are taken at the time of staging laparoscopy. Patients are then referred for neo-adjuvant therapy and tumour tissue, normal epithelium and background Barrett's oesophagus is collected upon completion of chemotherapy at the time of surgical resection. This work is covered under the generic Northern Ireland Biobank ethical approval and access to the tissues is governed by a peer-review application process administered by NIB (http://www.nibiobank.org/for-researchers).

Fresh tumour samples are also taken for the whole genome sequencing and the generation of near-patient in vitro models. This work is being carried out in collaboration with the Oesophageal Cancer Molecular and Clinical Stratification (OCCAMS) group as part of the International Cancer Genome Consortium (ICGC) and has been ethically approved (10/H0305/1). As well as signing a NIB consent form for the storage of tissue patients also receive an OCCAMS patient information sheet and sign an OCCAMS consent form to allow their tissue to be used in this collaborative project. Any research data generated will be stored for a period of 20 years.

The research described in WP3 involves the use of animal models of oesophageal squamous cell carcinoma in Trinity College Dublin. In accordance with **DIRECTIVE 2010/63/EU** all animal work will be pre-approved through ESR individual authorization with the national competent authority (Irish Medicines Board, S.I. No. 543 of 2012) and approval by the college Animal Research and Ethics Committee.

Addressing issues in the ethical issues table

Ethical issues of the research objectives and research methodology: TRACT intends to define new biomarkers in OOC and their relationship to disease progression and response to therapeutic intervention. Such data could have potential impact on OOC patients. The study of molecular biomarkers and mechanisms of drug resistance in oral squamous cell carcinoma is one of the research objectives of TRACT. To carry out these aspects of TRACT saliva and tissue samples will be recovered from patients undergoing routine procedures as part of their continuing care. Participants will be recruited sequentially from patients attending the dysplasia/oral medicine clinics in the Department of Oral and Maxillofacial Surgery at the Dublin Dental University Hospital and the Service of Stromatology and Maxillofacial Surgery at the University General Hospital Valencia. Suitable patients will be identified and informed consent will be obtained by the nominated gatekeeper (TBC in each location) when the patient is initially assessed at either Hospital. The patients will be provided with a consent form and information leaflet which clearly explains all that is required. The patients will then decide whether or not to participate in the study before the date of surgery. Non participation will not impact on the patient's treatment or scheduling of treatment. The time from assessment to treatment is at least 4-6 weeks in precancerous lesions and less than 4 weeks for oral cancer. The participant will be provided with the information at the assessment stage and permitted to consider the request for a minimum of 4 weeks prior to their treatment.

Patients will be asked to provide approximately 3-5ml of saliva. This will be achieved passively by allowing the saliva to passively drain from the lower lip into a plastic 15 ml conical tube every 30 seconds for 2 min. No physical intervention is required. It is hoped to receive consent from 30-50 patients displaying mild, moderate, severe dysplasia and OSSC patients. Normal (no signs of disease) age and sex matched controls will be recruited from patients undergoing routine dental check-ups/cleaning or orthodontic work.

Tissue biopsies and peripheral blood samples will be obtained from OSSC patients undergoing these procedures as part of their routine care and will be recruited from suitable patients as identified by the oral medicine teams in Dublin Dental University Hospital and the Service of Stromatology and Maxillofacial Surgery at the University General Hospital Valencia. After a full assessment of the tumour/lesion a sample will be taken in the form of a 5mm punch biopsy from an appropriate site, a second biopsy will be taken from a section of normal tissue and will serve as a control. As part of the routine procedure blood samples will be taken from all patients and one vial will be set aside for the study. There will be no increased risk for patients who would be undergoing these procedures as part of their normal treatment plan.

Each sample upon collection will be anonymised by the gatekeeper leaving no visible identifying personal patient details attached to any sample. Irrevocable anonymisation of personal data puts it outside data protection requirements as the data can no longer be linked to an individual and therefore cannot be considered to be personal data.

Where monitoring of patient status is required samples will be coded by the gatekeeper with using a predesigned key. The person who will hold the "key" or code=number=name to the participant will be the treating consultant and therefore already entitled to know the name of the participant. Therefore s/he should be the person who shall be referred to in case of need to re-identify a subject.

Consent forms will be hard copy consent forms and will be locked in a cupboard only accessible by the principle investigator and treating consultant. Electronic recording of laboratory results will be stored on an encrypted data storage device, which is only accessible by principle investigator.

Data will be retained until 5 years after completion of the study on encrypted password coded computers. Then it will be destroyed with the consent of the participants. Consent will be stored for the duration of the patient's life or for 8 years following death as per the Irish Dental/Medical Council Guidelines or equivalent.

Processing of these samples will be destructive in nature and will utilise all of the procured sample, therefore no saliva or tissue belonging to any of the patients will remain or will be stored after the completion of these studies. Should a patient wish to withdraw from the study after providing a sample that sample will be destroyed and disposed of in the appropriate manner immediately. Published data will not be provided to third parties. Some commercially available oral squamous cell carcinoma cell lines will also be used during the project. The oral epithelia Ca9.22 cell line will be sourced from the Health Science Research Resources Bank, Osaka, Japan and TR146 oral carcinoma and DOK dysplastic oral cell lines will be obtained from the collections help by Public Health England/ European Collection of Authenticated Cell Lines. TRACT will also have access to a panel of oesophageal adenocarcinoma cell lines again purchased from Public Health England/European Collection of Authenticated Cell Lines:

https://www.phe-culturecollections.org.uk/products/celllines/generalcell/oesophagealcelllines.jsp

OAC cell lines will include ES026 (adenocarcinoma of gastroesophageal junction), ES051 (distal oesophageal adenocarcinoma), OACM5.1C (Barret's adenocarcinoma), OE19 and OE33 (human Caucasian oesophageal carcinoma), SK-GT-4 (oesophagus, adenocarcinoma well-differentiated) and OACP4C (gastric cardia adenocarcinoma). In WP 3, CRISPR/Cas9 will be applied to OAC cell lines by ESR 7.

The primary objective of the research projects of ESR 2 and 4 based in QUB is to identify a molecular biomarker predictive of benefit from neo-adjuvant chemotherapy in early stage oesophageal adenocarcinoma. The secondary objective is the identification of genes and pathways associated with resistance to neo-adjuvant chemotherapy in oesophageal adenocarcinoma. Given the poor prognosis and the majority of patients for whom tissue samples will be utilised will be deceased. However, for surviving patients there is a potential for their tissue sample to be required for testing to guide the use of targeted therapeutic agents in the event that they experience a relapse. Therefore it will be mandatory that no tissue samples are exhausted during this study and that sufficient material be retained for possible future testing.

For the retrospective dataset held by QUB, Belfast, the Clinical Oncology Information System (COIS) will be used to identify patients who have received neo-adjuvant chemotherapy from 2004-2014. The relevant clinical information will be collected from the COIS system and pathology reports obtained from the LabCentre system. All confidential data will be held in password protected and encrypted files on a computer and external hard drive in the locked office of Dr Richard Turkington at the Centre for Cancer Research and Cell Biology, Queen's University Belfast. All data will be held in accordance with the NHS code of Confidentiality and the Data Protection Act. Given the high relapse rate and poor survival associated with oesophageal adenocarcinoma the majority of patients will have died prior to this study beginning and so it will not be possible to obtain consent for the use of tissue samples. Surviving patients may well have relapsed or be undergoing subsequent treatment so we do not think it would be appropriate to obtain consent from surviving patients due to the potential of causing unnecessary distress. This plan of research has been granted ethical approval by the Office for Research Ethics Committees Northern Ireland (ORECNI). For the prospective collection all data will be collected according to the standard operating procedures of the Northern Ireland Biobank.

With respect to the animal based tumour models it is not expected that the research objective (to assess new tumouricidal drugs) will give rise to ethical issues. ERSs participating in animal based experiments will have been trained on the LAST Ireland course, which is recognised by the national competent authority, the Health Products Regulatory Authority. Local technical and veterinary staff will provide training in animal handling and the use of tumour models. Prior to conducting the research the project will be required to be approved by the local AREC committee and for the individual ESR to be registered with and authorised by the Health Products Regulatory Authority. Details of planned experimental work on animals and care of animals are included below.

To evaluate novel inflammatory modulators/caspase inhibitors in animal model of Oesophageal Adenocarcinoma

Housing, husbandry and care conditions for the animals: Mice will be housed in the comparative medicine animal facility in the Trinity Biomedical Sciences Institute, Trinity College Dublin. Mice will be housed in stable, compatible groups in enclosures designed to cause minimum disturbance to the animals allowing them enough space for exercise, normal social behaviour (e.g. grooming, play) and the provision of enrichment which will help reduce the risk of social stress and aggression. Mice will be allowed enough height for rearing on the hind legs for scanning, exploration and play and adequate depth of appropriate substrate (e.g. 1cm depth of dust-free woodchip) for hygiene, comfort and to permit foraging and digging behaviour. Nesting material (e.g. shredded paper or soft wood) for comfort, to help regulate temperature and light levels, and to hide and retreat from cage mates or threatening stimuli will be provided. Mice will be housed under appropriate lighting levels and regimes and will be fed a varied diet. Mice will be handled gently and infrequently. Extraneous noise and ultrasound will be kept to a minimum.

Nature of Experiments: A subcutaneous xenograft model of oesophageal cancer cells in nude mice will be established similar to that reported in Cai et al., 2015 (Metformin Induced AMPK Activation, G0/G1 Phase Cell Cycle Arrest and the Inhibition of Growth of Oesophageal Squamous Cell Carcinomas In Vitro and In Vivo PLoS One, 10, 1-14). Eight-week-old male athymic nude mice will be purchased from Haarlan in the UK. Mice will be housed in the Comparative Medicine Animal Facility in the Trinity Biomedical Sciences Institute, Trinity College Dublin.

Early passage oesophageal squamous cells such as EC109 cells will be harvested and 1×10^6 cells will be implanted subcutaneously into each flank of each mouse. The cell line chosen will be based on results from in vitro cell culture experiments. Proposed severity banding for the procedure is mild. The animals will be randomized into control and experimental groups (7–10 mice per group). The treatment will be initiated approximately two weeks after implantation (once tumours are palpable i.e. approximately 4mm in diameter) and will be continued for 21 days. For administration of novel inflammatory/caspase inhibitors it is envisaged that they will be administered once every two days intra-tumourally. The doses and vehicle used will be based on results from the cell culture studies. The control group will receive vehicle only. Tumor volume will be measured with an external caliper every 2 days and will be calculated as $V = \pi/6(\text{length} \times \text{width} \times \text{depth})$. At end of study and following euthanasia of animals, tumours will be removed and immunohistochemistry will be performed on tumour tissues. Please see below details of the procedures and techniques to be used.

Procedures and techniques:

Procedure 1

Procedure 1	Implantation of oesophageal cells
Species	Athymic nude mice
Life stage	8 weeks
Technique	s.c injection into each flank with PBS (10µl) containing oesophageal cells (10^6) in the log phase of growth.

Frequency of procedure	Once
Duration of procedure	Approximately 4 minutes
Proposed severity classification	Mild
Humane endpoints	Mice will be sacrificed if/when tumours reach 1.5cm in diameter
Number of animals to be used	80
Justification/relevance of procedure	In order to form tumours mice must be injected with oesophageal cells
Adverse effect(s) of procedure on animal welfare	None expected. Any animal found in distress will be euthanized immediately. Symptoms of distress include decreased water and food consumption weight loss, an unkempt appearance or an increase/decrease in movement.
What is the fate of the animals at the end of the procedure?	Euthanasia
If the fate of the animals is euthanasia, please state the method of euthanasia	Cervical dislocation under isofluorene (5% in oxygen)

Procedure 2

Procedure	Treatment with novel modulator
Species	Athymic nude mice
Life stage	8 weeks
Technique	Intra-tumoural injection of modulator
Frequency of procedure	Once every two days
Duration of procedure	Approximately 4 minutes
Proposed severity classification	Mild
Humane endpoints	Mice will be sacrificed if/when tumours reach 1.5cm in diameter

Number of animals to be used	80
Justification/relevance of procedure	Mice must receive an intra-tumoural injection to assess the effects of the novel compound on tumour burden and on caspase/inflammatory marker expression
Adverse effect(s) of procedure on animal welfare	None expected. Any animal found in distress will be euthanized immediately. Symptoms of distress include decreased water and food consumption weight loss, an unkempt appearance or an increase/decrease in movement.
What is the fate of the animals at the end of the procedure?	Euthanasia
If the fate of the animals is euthanasia, please state the method of euthanasia	Cervical dislocation under isofluorene (5% in oxygen)

Details of policies in place to minimise animal suffering: On receipt of mice they will be allowed to recover from travel for a minimum of 1 week. Cell lines will be screened and will be free of contamination. OAC cells will be resuspended in warm PBS (200µl) to prevent discomfort upon administration. OAC cells will be administered by subcutaneous injection which will cause minimum pain. Novel modulators will be administered by intra-tumoural injection. The mice will be well restrained so that they cannot move during the procedure. This prevents traumatising the organs once the needle has been inserted. A new needle will be used for each animal, since this will reduce discomfort caused by the procedure and also reduce the risk of any injection-site infection. Any discomfort will be further reduced by injecting fluid that is at body temperature.
If multiple tumours become apparent, the combination of the two largest diameters will not be allowed to exceed 1.5cm. The health of the mice will be thoroughly monitored as health limitations may be evident before the tumour reaches the maximum standards as stated above. Some limitations may include mobility restriction, the inability to access food and water, pressure on internal organs or sensitive regions of the body, or body condition score (BCS) of <2. Animals displaying such signs will be euthanized even if the maximum tumour size has not been reached.

Implementation of the 3Rs:

Replacement: Only novel modulators/caspase inhibitors that have undergone a thorough investigation in *in vitro* cell culture models, the results of which indicate their potential to be used to treat oesophageal cancer, will be tested in animals. It is necessary to trial potential therapeutics in live animals to determine if the results correlate with those demonstrated *in vitro*, prior to clinical trials in humans.

Reduction: The minimal number of animals is being used without compromising the ability to perform meaningful scientific analyses. On the basis of a sample size calculation we require a total of 80 animals, with 7-10 animals per cohort (control and 3 doses of caspase inhibitor treated in one study and control and 3 doses of immunomodulator treated in a second study) to obtain powerful statistical data. The tumours need to be of a relatively uniform size prior to injection of the compounds, therefore we need to keep some mice in reserve. From experience some tumours may not be uniform in size. Drugs may only be injected when there is no significant difference in tumour volume between the control and the drug-treated groups. A sample size of 40 for each study will allow a minimum of 7 mice per group and up to 10 to allow for the similar tumour size in each mouse. When tumours reach 4mm in diameter, mice will be randomly assigned into control or treated group. Tumour volume will be measured at a number of time points and analysed by repeated measures ANOVA.
Given that the tumour volume will be measured every two days, we will compute a specific growth rate for tumours. This will provide a much more robust measure of tumour growth than a simple end-point measurement, and to a large extent factor for any initial differences in tumour size thereby addressing the concern of variation in tumour size between mice. Additionally we will use repeated measures of ANOVA with each time point as the repeated measure and with initial tumour volume as a covariate. This will make the most of all the data, and provide us with a single figure for the significance of treatment effect. Based on specific growth rates from Cai et al (2015) we will need 7 replicates for a power of at least 0.9.

Refinement: Animals provide an essential and powerful resource to investigate the efficacy of potential anti-tumour drugs. The murine cancer model is an extensively used in vivo model, with 99% of mouse genes having the equivalent in humans, the mouse model provides the most relevant setting to study and molecularly dissect the effects of novel therapeutics on the malignant phenotype (Gunter at al., 2002). It provides valuable pre-clinical data to support a hypothesis which has been vigorously tested in vitro. By undertaking thorough investigation though multiple cellular assays such as viability assays, flow cytometry, western blotting and transfections, we will ensure that only the most promising novel modulators will be further investigated therefore reducing the numbers of mice being used. In order to minimise harm to the animal, they will be allowed to recover for one week post transport to the comparative medicine animal facility in TCD. During the study mice will be vigorously monitored for signs of distress such as decreased water and food consumption, weight loss, an unkempt appearance, hunching, failure to groom or an increase/decrease in movement. Mice with developing tumours will be observed at least three times weekly until a palpable tumour nodule is present. Once the tumour is palpable (approximately 2 weeks), daily monitoring will be under taken. If tumour growth becomes rapid mice may be monitored twice daily. And animal found in distress will be euthanized immediately. Once tumours begin to develop in the mice, the animals will be monitored daily for any signs of distress, or twice daily if tumour growth becomes rapid. Animals will be humanely euthanised if any animals are found to experience unacceptable levels of distress or if tumour size approaches a predetermined unacceptable size. A veterinarian will be available throughout the study for consultation.

We commit to providing the following documents prior to commencement of study:

1) Authorisation for supply of animals
2) Authorisation for animal experiments
3) Copies of training certificates/personnel licences of involved staff

Potential ethical impact of the research: Patients will be providing biopsy samples with the potential to diagnose disease and therapeutic outcome. Therefore, participants will be provided with the maximum information on the implications of participation in a project, in clear and accessible format, and be allowed independent and informed decision-making on whether to participate. The information will include written details of risks and benefits in participating, and a guarantee of confidentiality. Each of the national competent bodies, in accordance with legislation, have established reporting systems for the notification of suspected Serious Adverse Reactions (SARs) and Serious Adverse Events (SAEs) associated with human tissues and cells.

Associated with document Ref. Ares(2016)3241025 - 07/07/2016

ESTIMATED BUDGET FOR THE ACTION (page 1 of 2)

		Estimated eligible[1] costs (per budget category)										Total costs	EU contribution		
		A. Costs for recruited researchers						B. Institutional costs					Reimbursement rate %	Maximum EU contribution[2]	Maximum grant amount[3]
		A.1. Living allowance		A.2. Mobility allowance		A.3. Family allowance		B.1. Research, training and networking costs		B.2. Management and indirect[4] costs					
	Number of units (person-months)	Form of costs[5]	Unit		Unit		Unit		Unit		Unit					
			Costs per unit[6]	Total a[7]	Costs per unit[6]	Total b[7]	Costs per unit[6,8]	Total c[7]	Costs per unit[6]	Total d[7]	Costs per unit[6]	Total e[7]	f = a+b +c +d+e	g	h	i
1. TCD	144.00	1. TCD	3110.00	508298.4	2400	86400	1000	36000	1800.00	259200.00	1200.00	172800.00	1062698.40	100.00	1062698.40	
2. OROBOROS	36.00	2. OROBOROS	3110.00	117334.08	600	21600	250	9000	1800.00	64800.00	1200.00	43200.00	255934.08	100.00	255934.08	
3. UVEG	72.00	3. UVEG	3110.00	218545.92	1200	43200	500	18000	1800.00	129600.00	1200.00	86400.00	495745.92	100.00	495745.92	
4. UNISI	72.00	4. UNISI	3110.00	238922.64	1200	43200	500	18000	1800.00	129600.00	1200.00	86400.00	516122.64	100.00	516122.64	
5. QUB	72.00	5. QUB	3110.00	269375.76	1200	43200	500	18000	1800.00	129600.00	1200.00	86400.00	546575.76	100.00	546575.76	
Total consortium	396.00	Total consortium		1352476.80		237600.00		99000.00		712800.00		475200.00	2877076.80	100.00	2877076.80	2877076.80

ESTIMATED BUDGET FOR THE ACTION (page 2 of 2)

1 See Article 6 for the eligibility conditions.
2 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).
3 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.
4 The indirect costs covered by the operating grant (received under any EU or Euratom funding programme; see Article 6.3(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 (i.e. the unit cost for management and indirect costs will be halved for person-months that are incurred during the period covered by the operating grant).
5 See Article 5 for the form of costs.
6 See Annex 2a 'Additional information on the estimated budget' for the details on the costs per unit.
7 Total = costs per unit x number of units (person-months)
8 The amount for the family allowance inserted by the system represents an average (with/without family). For the financial statements (Annex 4), this amount will be adjusted according to the actual family status of the recruited researchers (as specified in the 'researcher declaration').

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

OROBOROS INSTRUMENTS GmbH (OROBOROS) GMBH, FN193145M, established in SCHOPFSTRASSE 18, INNSBRUCK 6020, Austria, ATU49093608 ('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 721906 (‘the Agreement’)

between THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN **and** *the Research Executive Agency (REA) ('the Agency'), under the power delegated by the European Commission ('the Commission'),*

for the action entitled ‘Training in Cancer Mechanisms and Therapeutics (TRACT)’.

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

UNIVERSITAT DE VALENCIA (UVEG), Decreto Nr 128/2004 , established in AVENIDA BLASCO IBANEZ 13, VALENCIA 46010, Spain, ESQ4618001D ('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 721906 (‘the Agreement’)

between THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN **and** *the Research Executive Agency (REA) ('the Agency'), under the power delegated by the European Commission ('the Commission'),*

for the action entitled ‘Training in Cancer Mechanisms and Therapeutics (TRACT)’.

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

UNIVERSITA' DEGLI STUDI DI SIENA (UNISI), R.D. 13.10.1927 N. 2831, established in VIA BANCHI DI SOTTO 55, SIENA 53100, Italy, IT00273530527 ('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 721906 (‘the Agreement’)

between THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN **and** *the Research Executive Agency (REA) ('the Agency'), under the power delegated by the European Commission ('the Commission'),*

for the action entitled ‘Training in Cancer Mechanisms and Therapeutics (TRACT)’.

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

THE QUEEN'S UNIVERSITY OF BELFAST (QUB), XN45384, established in UNIVERSITY ROAD LANYON BUILDING, BELFAST BT7 1NN, United Kingdom, GB254799511 ('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 721906 (‘the Agreement’)

between THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN **and** *the Research Executive Agency (REA) ('the Agency'), under the power delegated by the European Commission ('the Commission'),*

for the action entitled ‘Training in Cancer Mechanisms and Therapeutics (TRACT)’.

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

ⓘ print format A4

MODEL ANNEX 4 FOR H2020 MSC-ITN — MULTI

FINANCIAL STATEMENT FOR BENEFICIARY [name] FOR REPORTING PERIOD [reporting period]

			Eligible[1] costs (per budget category)									EU contribution		
			A. Costs for recruited researchers						B. Institutional costs			Total costs	Reimbursement rate %	Maximum EU contribution	Requested EU contribution
			A.1 Living allowance		A.2 Mobility allowance		A.3 Family allowance		B.1. Research, training and networking costs		B2. Management and indirect[2] costs				
		Form of costs[3]	Unit		Unit		Unit		Unit		Unit				
Name of the fellows[6]	Number of units (person months)		Costs per unit[4]	Total a[5]	Costs per unit[4]	Total b[5]	Costs per unit[4]	Total c[5]	Costs per unit[4]	Total d[5]	Costs per unit[4]	Total e[5]	f = a+b+c+d+e	g	h	i
Total beneficiary		**Total beneficiary**														

Checkbox 1:	I confirm that the total amount of the allowances used (including compulsory deductions) for the researcher is equal to or higher than the living allowance, the mobility allowance and the family allowance as set out in Annex 2 of the Agreement or that any underpayments in Reporting Period 1 will be corrected by the end of the action.

Checkbox 2 :	Did you receive any EU/Euratom operating grant during this reporting period? YES ❑ NO ❑ If yes, pls indicate how many of the total person-months (see 'total beneficiary' above) were incurred DURING the period covered by the operating grant?	Number of person-months	

The beneficiary 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).

ⓘ Please declare all person-months, even if you exceed the estimated budget (see Annex 2). Only person-months 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 6.3(b)). If you have received an operating grant during this reporting period, indirect costs will not be reimbursed for the person-months incurred during the period covered by the operating grant.

[3] See Article 5 for the forms of costs

[4] See Annex 2a 'Additional information on the estimated budget' for the details on the costs per unit.

[5] Total = costs per unit x number of units (person-months)

[6] Name of the researcher and related units for living (A.1) and family (A.3) allowances will be prefilled on the basis of the information provided by the beneficiary in the 'researcher declaration'

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