Document updated on 2018-10-24

The document starting on p. 3 of this PDF file is a heavily redacted version of the grant agreement for the Autism Innovative Medicine Studies-2-Trials (AIMS-2-Trials) research project. This file contains a 112-page document that replaces an earlier one of 664 pages.

I have updated this file following the request, below, from the IMI2 JU Access to Documents Team sent on 2018-10-22.

Panda Mery

> It has come to our attention that, contrary to what was stated in the letter responding to your first request of access to document, the file named 'Full grant agreement redacted' sent to you on 10 September 2018 included the annex 1 of the AIMS 2 TRIALS of the grant agreement. This information was shared with you inadvertently.
>
> **By publishing it on the internet this is now disclosing sensitive commercial information and personal data which were not intended for publication and for which you do not have any right to publish.**
>
> We therefore have to ask you to immediately remove the file from your internet page at the following link: http://gizmonaut.net/autism-documents/Full-Grant-Agreement-777394-AIMS-2-TRIALS_redacted.pdf.
>
> Please confirm that you will proceed as requested by replying to this email. Please do not hesitate to contact us by phone in case any clarification is needed.
>
> Thank you very much for your understanding and cooperation on this sensitive matter.

Followed on 2018-10-23 by:

> Thank you very much for your prompt reply and understanding.
>
> For the sake of clarity, attached hereto are:
>
> 1. The letter of reply to your initial application, informing you of the following:
>
> - the Grant Agreement was partially disclosed with redaction of commercially sensitive information and personal data of the individuals;
> - Annex 1 was withheld in its entirety considering that access to a redacted document would be meaningless;

- Annex 2 was withheld because it contains commercially sensitive information;
- Annex 3 contains personal data of individuals. Therefore, the hyperlink to the relevant template was provided.
- the remaining Annexes (4, 5 and 6) were provided as templates via a hyperlink.

2. The letter of reply to your confirmatory application, granting you access to the following:

- the ethics-related excerpt of ANNEX I of the AIMS-2-TRIALS Grant Agreement (partly redacted);
- Work Package 7, described in Annex 1 of the AIMS-2-TRIALS Grant Agreement.

3. In one consolidated file (for ease of use), the three documents to which access was granted to you based on the two above-referenced official letters (in particular, as explained above, only the core text of the Grant Agreement (Articles 1 to 57, pages 1 to 88), and the relevant part of Annex 1, *ie* Work Package 7 related to ethics (pages 59 and 60 of Annex 1), and the Ethics section (pages 149 to 170)).

As explained in our previous email, unfortunately, the document sent to you in response to your initial application did not reflect the IMI2 JU's decision on your application.
Therefore, given the sensitive nature of the commercial and personal data included in the document in question, this document must be immediately removed from your website and any other web-based platforms, and any copies thereof deleted.

Accordingly, we would like to ask you to please:

- remove this document from your website today (you are free to replace the document initially shared with you by the consolidated one attached to this email [GA_WP7_Ethics_AIMS2TRIAL.pdf]);
- inform anyone to whom you may have directly sent the document of their obligation to delete it from their respective records.

We thank you for your valuable cooperation and apologise for any inconvenience this may have caused.

GRANT AGREEMENT

NUMBER — 777394 — AIMS-2-TRIALS

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

on the one part,

the **Innovative Medicines Initiative 2 Joint Undertaking** ('the JU'),

represented for the purposes of signature of this Agreement by the JU Executive Director or his/her representative, Pierre MEULIEN,

and

on the other part,

1. 'the coordinator':

KING'S COLLEGE LONDON (KCL), established in Strand, LONDON WC2R 2LS, United Kingdom, VAT number: [redacted], represented for the purposes of signing the Agreement by [redacted]

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

2. ***F. HOFFMANN-LA ROCHE AG (ROCHE)****, established in GRENZACHERSTRASSE 124, BASEL 4070, Switzerland, VAT number:* [redacted], as 'beneficiary not receiving EU funding' (see Article 9),

3. **THE CHANCELLOR MASTERS AND SCHOLARS OF THE UNIVERSITY OF CAMBRIDGE (UCAM)**, established in TRINITY LANE THE OLD SCHOOLS, CAMBRIDGE CB2 1TN, United Kingdom, VAT number: [redacted],

4. **STICHTING KATHOLIEKE UNIVERSITEIT (RUMC)**, established in GEERT GROOTEPLEIN NOORD 9, NIJMEGEN 6525 EZ, Netherlands, VAT number: [redacted],

5. **SERVICIO MADRILENO DE SALUD (SERMAS)**, established in PLAZA CARLOS TRIAS BERTRAN 7, MADRID 28020, Spain, VAT number: [redacted],

6. **INSTITUT PASTEUR (IP)**, established in RUE DU DOCTEUR ROUX 25-28, PARIS CEDEX 15 75724, France, VAT number: [redacted],

7. **UNIVERSITAT BASEL (UNIBAS)**, established in PETERSPLATZ 1, BASEL 4051, Switzerland, VAT number: [redacted],

8. **ZENTRALINSTITUT FUER SEELISCHE GESUNDHEIT (CIMH)**, established in Square J 5, MANNHEIM 68159, Germany, VAT number: [redacted],

9. **BIOSCI CONSULTING (BIOSCI)**, established in Weg Naar Geneuth 95, Maasmechelen 3631, Belgium, VAT number: [redacted],

10. **RIJKSUNIVERSITEIT GRONINGEN (RG)**, established in Broerstraat 5, GRONINGEN 9712CP, Netherlands, VAT number: [redacted],

11. **THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD (UOXF)**, established in WELLINGTON SQUARE UNIVERSITY OFFICES, OXFORD OX1 2JD, United Kingdom, VAT number: [redacted],

12. **INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)**, established in RUE DE TOLBIAC 101, PARIS 75654, France, VAT number: [redacted],

13. **THE UNIVERSITY OF EDINBURGH (UEDIN)**, established in OLD COLLEGE, SOUTH BRIDGE, EDINBURGH EH8 9YL, United Kingdom, VAT number: [redacted],

14. **ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS (APHP)**, established in 3 Avenue Victoria, PARIS 75004, France, VAT number: [redacted],

15. **THE PROVOST, FELLOWS, FOUNDATION SCHOLARS & THE OTHER MEMBERS OF BOARD OF THE COLLEGE OF THE HOLY & UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN (TCD)**, established in College Green, DUBLIN 2, Ireland, VAT number: [redacted]

16. **BIRKBECK COLLEGE - UNIVERSITY OF LONDON (BC)**, established in MALET STREET, LONDON WC1E 7HX, United Kingdom, VAT number: [redacted],

17. **STICHTING BURO ECNP (ECNP)**, established in BOLOGNALAAN 28, UTRECHT 3584 CJ, Netherlands, VAT number: [redacted],

18. **NOLDUS INFORMATION TECHNOLOGY BV (NOLDUS)**, established in NIEUWE KANAAL 5, WAGENINGEN 6709 PA, Netherlands, VAT number: [redacted],

19. **ARTTIC (ARTTIC)**, established in RUE DU DESSOUS DES BERGES 58A, PARIS 75013, France, VAT number: [redacted],

20. **DEMCON ADVANCED MECHATRONICS BV (DEMCON)**, established in INSTITUTENWEG 25, ENSCHEDE 7521 PH, Netherlands, VAT number: [redacted],

21. **KAROLINSKA INSTITUTET (KI)**, established in Nobels Vag 5, STOCKHOLM 17177, Sweden, VAT number: [redacted],

22. **JOHANN WOLFGANG GOETHE-UNIVERSITATFRANKFURT AM MAIN (GU)**, established in THEODOR W ADORNO PLATZ 1, FRANKFURT AM MAIN 60629, Germany, VAT number: [redacted],

23. **UNIVERSITAIR MEDISCH CENTRUM UTRECHT (UMCU)**, established in HEIDELBERGLAAN 100, UTRECHT 3584 CX, Netherlands, VAT number: [redacted],

24. **UNIVERSITEIT GENT (UGent)**, established in SINT PIETERSNIEUWSTRAAT 25, GENT 9000, Belgium, VAT number: [redacted],

25. **UNIVERSITY OF NEWCASTLE UPON TYNE (UNEW)**, established in KINGS GATE, NEWCASTLE UPON TYNE NE1 7RU, United Kingdom, VAT number: [redacted],

26. **UNIVERSITAET ULM (UULM)**, established in HELMHOLTZSTRASSE 16, ULM 89081, Germany, VAT number: [redacted],

27. **CENTRE HOSPITALIER REGIONAL UNIVERSITAIRE DE TOURS (CHUT)**, established in BOULEVARD TONELLE 2, TOURS CEDEX 9 37044, France,

28. **KLINIKUM RECHTS DER ISAR DER TECHNISCHEN UNIVERSITAT MUNCHEN (TUM-MED)**, established in ISMANINGER STRASSE 22, MUENCHEN 81675, Germany, VAT number: [redacted],

29. **Fondazione Stella Maris (FSM)**, established in Viale del Tirreno 331, Pisa 56118, Italy, VAT number: [redacted],

30. **UNIVERSIDAD DE SALAMANCA (USAL)**, established in CALLE PATIO DE ESCUELAS 1, SALAMANCA 37008, Spain, VAT number: [redacted],

31. **UNIVERSITY OF GLASGOW (UGLA)**, established in UNIVERSITY AVENUE, GLASGOW G12 8QQ, United Kingdom, VAT number: [redacted],

32. **COMMISSARIAT A L ENERGIE ATOMIQUE ET AUX ENERGIES ALTERNATIVES (CEA)**, established in RUE LEBLANC 25, PARIS 15 75015, France, VAT number: [redacted],

33. **UNIVERSITAETSMEDIZIN GOETTINGEN - GEORG-AUGUST-UNIVERSITAET GOETTINGEN - STIFTUNG OEFFENTLICHEN RECHTS (UMG-GOE)**, established in Robert-Koch-Strasse 40, GOETTINGEN 37075, Germany, VAT number: [redacted],

34. **STELLENBOSCH UNIVERSITY (SU)**, established in VICTORIA STREET ADMINISTRATION B BUILDING, STELLENBOSCH 7600, South Africa, VAT number: [redacted],

35. **UPPSALA UNIVERSITET (UU)**, established in VON KRAEMERS ALLE 4, UPPSALA 751 05, Sweden, VAT number: [redacted],

36. **UNIVERSIDADE DE COIMBRA (UC)**, established in PACO DAS ESCOLAS, COIMBRA 3001 451, Portugal, VAT number: [redacted],

37. **FUNDAZIOA POLICLINICA GIPUZKOA FUNDACION (FPGF)**, established in PASEO MIRAMON 174, SAN SEBASTIAN 20014, Spain, VAT number: [redacted],

38. **FUNDACIO CLINIC PER A LA RECERCA BIOMEDICA (FCRB)**, established in CARRER ROSSELLO 149, BARCELONA 08036, Spain, VAT number: [redacted],

*39. **JANSSEN PHARMACEUTICA NV (JANSSEN)**, established in TURNHOUTSEWEG 30, BEERSE 2340, Belgium, VAT number:* [redacted], as 'beneficiary not receiving EU funding' (see Article 9),

*40. **NOVARTIS PHARMA AG (NOVARTIS)**, established in LICHTSTRASSE 35, BASEL 4056, Switzerland, VAT number:* [redacted], as 'beneficiary not receiving EU funding' (see Article 9),

41. ***UCB BIOPHARMA SPRL (UCB)****, established in ALLEE DE LA RECHERCHE 60, BRUSSELS 1070, Belgium, VAT number:* [redacted], as 'beneficiary not receiving EU funding' (see Article 9),

42. ***TEVA PHARMACEUTICAL INDUSTRIES LIMITED (Teva)****, established in 5 BASEL ST, PETACH TIVKA 49131, Israel, VAT number:* [redacted], as 'beneficiary not receiving EU funding' (see Article 9),

43. ***AUTISM SPEAKS INC. NON PROFIT CORPORATION (AUTISM SPEAKS)****, established in State Road FLOOR 2 1060, Princeton NJ 08540, United States,* as 'beneficiary not receiving EU funding' (see Article 9),

44. ***THE SIMONS FOUNDATION, INC (SFARI)****, established in 160 FIFTH AVENUE, 7TH FLOOR, NEW YORK 10010, United States,* as 'beneficiary not receiving EU funding' (see Article 9),

45. ***AUTISTICA (Autistica)****, established in ST SAVIOUR'S HOUSE 39-41 UNION STREET, LONDON SE1 1SD, United Kingdom,* as 'beneficiary not receiving EU funding' (see Article 9),

46. **AUTISME-EUROPE AISBL (AE)**, established in RUE MONTOYER 39, BRUXELLES 1000, Belgium, VAT number: [redacted],

47. **UNIVERSITY OF BRISTOL (UNIVBRIS)**, established in TYNDALL AVENUE SENATE HOUSE, BRISTOL BS8 1TH, United Kingdom, VAT number: [redacted],

48. **STARLAB BARCELONA SL (STARLAB)**, established in AVENIDA TIBIDABO 47 BIS, BARCELONA 08035, Spain, VAT number: [redacted],

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.

The JU receives contributions from the European Union's Horizon 2020 research and innovation programme and support from European Federation of Pharmaceutical Industries and Associations (EFPIA) and from **AUTISM SPEAKS INC. NON PROFIT CORPORATION (AUTISM SPEAKS), AUTISTICA (Autistica), The Simons Foundation, Inc (SFARI)**.

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

2a Additional information on the estimated budget

Annex 3 Accession Forms

3a Declaration on joint and several liability of linked third parties

Annex 4 Model for the financial statements

Annex 5 Model for the certificate on the financial statements

Annex 6 Model for the certificate on the methodology

TERMS AND CONDITIONS

TABLE OF CONTENTS

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 '**Autism Innovative Medicine Studies – 2 – Trials**' — '**AIMS-2-TRIALS**' **('action')**, as described in Annex 1.

ARTICLE 3 — DURATION AND STARTING DATE OF THE ACTION

The duration of the action will be **60 months** as of 1 June 2018 ('**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 linked third party) and budget category (see Articles 5, 6, and 14). It also shows the estimated costs of the beneficiaries not receiving JU funding (see Article 9).

4.2 Budget transfers

The estimated budget breakdown indicated in Annex 2 may be adjusted — without an amendment (see Article 55) — by transfers of amounts between beneficiaries, budget categories and/or forms of costs set out in Annex 2, if the action is implemented as described in Annex 1.

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

CHAPTER 3 GRANT

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

5.1 Maximum grant amount

The '**maximum grant amount**' is **EUR 54,999,998.75** (fifty four million nine hundred and ninety nine thousand nine hundred and ninety eight EURO and seventy five eurocents).

5.2 Form of grant, reimbursement rates and forms of costs

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

The estimated eligible costs of the action are EUR **55,112,998.75** (fifty five million one hundred and twelve thousand nine hundred and ninety eight EURO and seventy five eurocents).

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

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

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

Personnel **costs for SME owners** not receiving a salary (see Article 6.2, Point A.4) must be declared on the basis of the amount per unit set out in Annex 2a (**unit costs**);

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

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

(d) for **other direct costs**:

- for costs of internally invoiced goods and services: on the basis of an amount per unit calculated by the beneficiary in accordance with its usual cost accounting practices (‘**unit costs**’);
- for all other costs: as actually incurred costs (**actual costs**);

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

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

5.3 Final grant amount — Calculation

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

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

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

Step 2 – Limit to the maximum grant amount

Step 3 – Reduction due to the no-profit rule

Step 4 – Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

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

The reimbursement rate(s) (see Article 5.2) are applied to the eligible costs (actual costs, unit costs

and flat-rate costs; see Article 6) declared by the beneficiaries and linked third parties (see Article 20) and approved by the JU (see Article 21).

5.3.2 Step 2 — Limit to the maximum grant amount

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

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

The grant must not produce a profit.

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

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

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

The following are considered **receipts**:

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

(b) financial contributions to the beneficiary or to a linked third party specifically to be used for the action, given by:

(i) a third party or

(ii) a beneficiary not receiving JU funding which is:

- a JU member or a constituent or affiliated entity of a JU member or
- a JU associated partner or a constituent or affiliated entity of a JU associated partner, and

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

The following are however not considered receipts:

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

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

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

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

5.3.4 Step 4 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations — Reduced grant amount — Calculation

If the grant is reduced (see Article 43), the JU will calculate the reduced grant amount by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the maximum grant amount set out in Article 5.1.

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

- the amount obtained following Steps 1 to 3 or
- the reduced grant amount following Step 4.

5.4 Revised final grant amount — Calculation

If — after the payment of the balance (in particular, after checks, reviews, audits or investigations; see Article 22) — the JU 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 JU 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 JU 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 the seriousness of the errors, irregularities or fraud or breach of obligations (see Article 43.2).

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

ARTICLE 6 — ELIGIBLE AND INELIGIBLE COSTS

6.1 General conditions for costs to be eligible

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

(a) for **actual costs**:

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

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

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

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

(v) they must be identifiable and verifiable, in particular recorded in the beneficiary's accounts

in accordance with the accounting standards applicable in the country where the beneficiary is established and with the beneficiary's usual cost accounting practices;

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

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

(b) for **unit costs**:

(i) they must be calculated as follows:

{amounts per unit set out in Annex 2a or calculated by the beneficiary in accordance with its usual cost accounting practices (see Article 6.2, Point A and Article 6.2.D.5)

multiplied by

the number of actual units};

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

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

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

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

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

6.2 Specific conditions for costs to be eligible

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

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

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

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

A. Direct personnel costs

Types of eligible personnel costs

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

Beneficiaries that are non-profit legal entities[1] may also declare as personnel costs **additional remuneration** for personnel assigned to the action (including payments on the basis of supplementary contracts regardless of their nature), if:

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

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

'Additional remuneration' means any part of the remuneration which exceeds what the person would be paid for time worked in projects funded by national schemes.

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

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

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

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

{{EUR 8 000

divided by

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

multiplied by

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

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

(a) the person works under conditions similar to those of an employee (in particular regarding the way the work is organised, the tasks that are performed and the premises where they are performed);

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

(b) the result of the work carried out belongs to the beneficiary (unless exceptionally agreed otherwise), and

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

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

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

A.5 **Costs of 'beneficiaries that are natural persons'** Not applicable.

Calculation

Personnel costs must be calculated by the beneficiaries as follows:

{{hourly rate

multiplied by

the number of actual hours worked on the action},

plus

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

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

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

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

minus

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

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

(a) for personnel costs declared as **actual costs** (i.e. budget categories A.1, A.2, A.3): the hourly rate is calculated *per full financial year*, as follows:

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

divided by

number of annual productive hours}

using the personnel costs and the number of productive hours for each full financial year

covered by the reporting period concerned. If a financial year is not closed at the end of the reporting period, the beneficiaries must use the hourly rate of the last closed financial year available.

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

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

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

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

plus

overtime worked

minus

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

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

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

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

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

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

As an alternative, beneficiaries may calculate the hourly rate *per month*, as follows:

{actual monthly personnel cost (excluding additional remuneration) for the person

divided by

{number of annual productive hours / 12}}

using the personnel costs for each month and (one twelfth of) the annual productive hours calculated according to either option (i) or (iii) above, i.e.:

- fixed number of hours or
- standard annual productive hours.

Time spent on **parental leave** may not be deducted when calculating the hourly rate per month. However, beneficiaries may declare personnel costs incurred in periods of parental leave in proportion to the time the person worked on the action in that financial year.

If parts of a basic remuneration are generated over a period longer than a month, the beneficiaries may include only the share which is generated in the month (irrespective of the amount actually paid for that month).

Each beneficiary must use only one option (per full financial year or per month) for each full financial year;

(b) for personnel costs declared on the basis of **unit costs** (i.e. budget categories A.1, A.2, A.4): the hourly rate is one of the following:

(i) for SME owners the hourly rate set out in Annex 2a (see Point A.4 above), or

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

- the cost accounting practices used are applied in a consistent manner, based on objective criteria, regardless of the source of funding;
- the hourly rate is calculated using the actual personnel costs recorded in the beneficiary's accounts, excluding any ineligible cost or costs included in other budget categories.

  The actual personnel costs may be adjusted by the beneficiary on the basis of budgeted or estimated elements. Those elements must be relevant for calculating the personnel costs, reasonable and correspond to objective and verifiable information;

and

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

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

C. Direct costs of providing financial support to third parties

Not applicable

D. Other direct costs

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

D.2 The **depreciation costs of equipment, infrastructure or other assets** (new or second-hand) as recorded in the beneficiary's accounts are eligible, if they were purchased in accordance with

Article 10.1.1 and written off in accordance with international accounting standards and the beneficiary's usual accounting practices.

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

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

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

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

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

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

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

D.4 **Capitalised and operating costs of 'large research infrastructure'**[2] directly used for the action are eligible, if:

(a) the value of the large research infrastructure represents at least 75% of the total fixed assets (at historical value in its last closed balance sheet before the date of the signature of the Agreement or as determined on the basis of the rental and leasing costs of the research infrastructure[3]);

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

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

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

[3] For the definition, see Article 2(6) of the H2020 Framework Programme Regulation No 1291/2013: '**Research infrastructure**' are facilities, resources and services that are used by the research communities to conduct research and foster innovation in their fields. Where relevant, they may be used beyond research, e.g. for education or public services. They include: major scientific equipment (or sets of instruments); knowledge-based resources such as collections, archives or scientific data; e-infrastructures such as data and computing systems and communication networks; and any other infrastructure of a unique nature essential to achieve excellence in research and innovation. Such infrastructures may be 'single-sited', 'virtual' or 'distributed'.

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

D.5 **Costs of internally invoiced goods and services** directly used for the action are eligible, if:

(a) they are declared on the basis of a unit cost calculated in accordance with the beneficiary's usual cost accounting practices;

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

(c) the unit cost is calculated using the actual costs for the good or service recorded in the beneficiary's accounts, excluding any ineligible cost or costs included in other budget categories.

The actual costs may be adjusted by the beneficiary on the basis of budgeted or estimated elements. Those elements must be relevant for calculating the costs, reasonable and correspond to objective and verifiable information;

(d) the unit cost excludes any costs of items which are not directly linked to the production of the invoiced goods or service.

'Internally invoiced goods and services' means goods or services which are provided by the beneficiary directly for the action and which the beneficiary values on the basis of its usual cost accounting practices.

E. Indirect costs

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

(a) costs of subcontracting and

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

(c) not applicable;

(d) not applicable.

Beneficiaries receiving an operating grant[4] financed by the EU or Euratom budget cannot declare indirect costs for the period covered by the operating grant, unless they can demonstrate that the operating grant does not cover any costs of the action.

F. Specific cost category(ies)

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

Not applicable

6.3 Conditions for costs of linked third parties to be eligible

Costs incurred by linked third parties are eligible if they fulfil — mutatis mutandis — the general and specific conditions for eligibility set out in this Article (Article 6.1 and 6.2) and Article 14.1.1.

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

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

6.5 Ineligible costs

'**Ineligible costs**' are:

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

(i) costs related to return on capital;

(ii) debt and debt service charges;

(iii) provisions for future losses or debts;

(iv) interest owed;

(v) doubtful debts;

(vi) currency exchange losses;

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

(viii) excessive or reckless expenditure;

(ix) deductible VAT;

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

(b) costs declared under another JU, EU or Euratom grant (including other grants awarded by the JU, grants awarded by a Member State and financed by the EU or Euratom budget and grants awarded by bodies other than the JU for the purpose of implementing the EU or Euratom budget); in particular, indirect costs if the beneficiary is already receiving an operating grant financed by the EU or Euratom budget in the same period, unless it can demonstrate that the operating grant does not cover any costs of the action.

6.6 Consequences of declaration of ineligible costs

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

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

CHAPTER 4 RIGHTS AND OBLIGATIONS OF THE PARTIES

SECTION 1 RIGHTS AND OBLIGATIONS RELATED TO IMPLEMENTING THE ACTION

ARTICLE 7 — GENERAL OBLIGATION TO PROPERLY IMPLEMENT THE ACTION

7.1 General obligation to properly implement the action

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

7.2 Consequences of non-compliance

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

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

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

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

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

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

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

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

9.1 Rules for the implementation of action tasks by beneficiaries not receiving JU funding

Beneficiaries that are not eligible for JU funding (‘**beneficiaries not receiving JU funding**’) must implement the action tasks attributed to them in Annex 1 in accordance with Article 7.1.

Their costs are estimated in Annex 2 but:

- will not be reimbursed and
- will not be taken into account for the calculation of the grant (see Articles 5.2, 5.3 and 5.4, and 21).

Chapter 3, Articles 10 to 15, 18.1.2, 20.3(b), 20.4(b), 20.6, 21, 23a, 26.4, 27.2, 28.1 (with the exception of additional exploitation obligations), 28.2, 30.3, 31.5, 40, 42, 43, 44, 47 and 48 do not apply to these beneficiaries.

They will not be subject to financial checks, reviews and audits under Article 22.

Beneficiaries not receiving JU funding may provide in-kind contributions to another beneficiary. In this case, they will be considered as a third party for the purpose of Articles 11 and 12.

9.2 Consequences of non-compliance

If a beneficiary not receiving JU funding breaches any of its obligations under this Article, its participation in the Agreement may be terminated (see Article 50).

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

ARTICLE 10 — PURCHASE OF GOODS, WORKS OR SERVICES

10.1 Rules for purchasing goods, works or services

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

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

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

10.1.2 Beneficiaries that are 'contracting authorities' within the meaning of Directive 2004/18/EC[5] (or 2014/24/EU[6]) or 'contracting entities' within the meaning of Directive 2004/17/EC[7] (or 2014/25/EU[8]) must comply with the applicable national law on public procurement.

10.2 Consequences of non-compliance

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

[6] Directive 2014/24/EU of the European Parliament and of the Council of 26 February 2014 on public procurement and repealing Directive 2004/18/EC. (OJ L 94, 28.03.2014, p. 65).

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

[8] Directive 2014/25/EU of the European Parliament and of the Council of 26 February 2014 on procurement by entities operating in the water, energy, transport and postal services sectors and repealing Directive 2004/17/EC (OJ L 94, 28.03.2014, p. 243).

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

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

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

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

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

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

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

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

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

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

11.2 Consequences of non-compliance

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

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

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

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

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

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

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

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

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

12.2 Consequences of non-compliance

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

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

ARTICLE 13 — IMPLEMENTATION OF ACTION TASKS BY SUBCONTRACTORS

13.1 Rules for subcontracting action tasks

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

Subcontracting may cover only a limited part of the action.

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

The tasks to be implemented and the estimated cost for each subcontract must be set out in Annex 1 and the total estimated costs of subcontracting per beneficiary must be set out in Annex 2. The JU may however approve subcontracts not set out in Annex 1 and 2 without amendment (see Article 55), if:

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

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

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

Beneficiaries that are ‘contracting authorities’ within the meaning of Directive 2004/18/EC (or 2014/24/EU) or ‘contracting entities’ within the meaning of Directive 2004/17/EC (or 2014/25/EU) must comply with the applicable national law on public procurement.

13.2 Consequences of non-compliance

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

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

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

ARTICLE 14 — IMPLEMENTATION OF ACTION TASKS BY LINKED THIRD PARTIES

14.1 Rules for calling upon linked third parties to implement part of the action

14.1.1 The following **affiliated entities**[10] and **third parties with a legal link to a beneficiary**[11] (‘**linked third parties**’) may implement the action tasks attributed to them in Annex 1:

- GREATER GLASGOW HEALTH BOARD (GGHB), affiliated or linked to UGLA, if it has accepted joint and several liability with the beneficiary (see Annex 3a)

The linked third parties may declare as eligible the costs they incur for implementing the action tasks in accordance with Article 6.3.

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

14.1.2 The beneficiaries must ensure that their obligations under Articles 18, 20, 35, 36 and 38 also apply to their linked third parties.

14.2 Consequences of non-compliance

If any obligation under Article 14.1.1 is breached, the costs of the linked third party will be ineligible (see Article 6) and will be rejected (see Article 42).

If any obligation under Article 14.1.2 is breached, the grant may be reduced (see Article 43).

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

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[10] For the definition see Article 2.1(2) 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
- directly or indirectly controlling a participant.

‘Control’ may take any of the following forms:
(a) the direct or indirect holding of more than 50% of the nominal value of the issued share capital in the legal entity concerned, or of a majority of the voting rights of the shareholders or associates of that entity;
(b) the direct or indirect holding, in fact or in law, of decision-making powers in the legal entity concerned.

However the following relationships between legal entities shall not in themselves be deemed to constitute controlling relationships:
(a) the same public investment corporation, institutional investor or venture-capital company has a direct or indirect holding of more than 50% of the nominal value of the issued share capital or a majority of voting rights of the shareholders or associates;
(b) the legal entities concerned are owned or supervised by the same public body.

[11] ‘**Third party with a legal link to a beneficiary**’ is any legal entity which has a legal link to the beneficiary implying collaboration that is not limited to the action.

ARTICLE 14a — IMPLEMENTATION OF ACTION TASKS BY INTERNATIONAL PARTNERS

Not applicable

ARTICLE 15 — FINANCIAL SUPPORT TO THIRD PARTIES

15.1 Rules for providing financial support to third parties

Not applicable

15.2 Financial support in the form of prizes

Not applicable

15.3 Consequences of non-compliance

Not applicable

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

16.1 Rules for providing trans-national access to research infrastructure

Not applicable

16.2 Rules for providing virtual access to research infrastructure

Not applicable

16.3 Consequences of non-compliance

Not applicable

SECTION 2 RIGHTS AND OBLIGATIONS RELATED TO THE GRANT ADMINISTRATION

ARTICLE 17 — GENERAL OBLIGATION TO INFORM

17.1 General obligation to provide information upon request

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

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

Each beneficiary must keep information stored in the Participant Portal 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 JU 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 or JU's financial interests, in particular:

(i) changes in its legal, financial, technical, organisational or ownership situation or those of its linked third parties and

(ii) changes in the name, address, legal form, organisation type of its linked third parties;

(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 Article 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 JU or the Commission may accept non-original documents if it considers that they offer a comparable level of assurance.

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

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

18.1.2 Records and other documentation to support the costs declared

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

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

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

In addition, **for unit costs calculated in accordance with the beneficiary's usual cost accounting practices**, the beneficiaries must keep adequate records and documentation to prove that the cost accounting practices used comply with the conditions set out in Article 6.2.

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

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

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

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

For costs declared by linked third parties (see Article 14), it is the beneficiary that must keep the originals of the financial statements and the certificates on the financial statements of the linked third parties.

18.2 Consequences of non-compliance

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

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

ARTICLE 19 — SUBMISSION OF DELIVERABLES

19.1 Obligation to submit deliverables

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

19.2 Consequences of non-compliance

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

ARTICLE 20 — REPORTING — PAYMENT REQUESTS

20.1 Obligation to submit reports

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

20.2 Reporting periods

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

- RP1: from month 1 to month 12
- RP2: from month 13 to month 24
- RP3: from month 25 to month 36
- RP4: from month 37 to month 48
- RP5: from month 49 to month 60

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 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**'.

The report must indicate the communication activities;

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

(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 JU and the Horizon 2020 key performance indicators and JU and the Horizon 2020 monitoring requirements;

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

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

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

The beneficiaries and linked third parties must declare all eligible costs, even if — for actual costs, unit costs and flat-rate costs — they exceed the amounts indicated in the estimated budget (see Annex 2). Amounts which are not declared in the individual financial statement will not be taken into account by the JU.

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 and each linked third party must **certify** that:

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

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

(iii) not applicable;

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

20.4 Final report — Request for payment of the balance

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

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

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

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

(ii) the conclusions on the action, and

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

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

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

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

20.5 Information on cumulative expenditure incurred

Not applicable

20.6 Currency for financial statements and conversion into euro

Financial statements must be drafted in euro.

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

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

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

20.7 Language of reports

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

20.8 Consequences of non-compliance

If the reports submitted do not comply with this Article, the JU 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, the JU may terminate the Agreement (see Article 50) or apply any of the other measures described in Chapter 6.

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 JU until the payment of the balance.

The amount of the pre-financing payment will be EUR **17,599,999.60** (seventeen million five hundred and ninety nine thousand nine hundred and ninety nine EURO and sixty eurocents).

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

An amount of EUR **2,749,999.94** (two million seven hundred and forty nine thousand nine hundred and ninety nine EURO and ninety four eurocents), corresponding to 5% of the maximum grant amount (see Article 5.1), is retained by the JU 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 JU 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 JU 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 and the linked third parties (see Article 20) and approved by the JU (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 JU 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 JU 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 beneficiaries' consent — against any other amount owed by a beneficiary to the JU up to the maximum JU contribution indicated, for that beneficiary, in the estimated budget (see Annex 2).

21.5 Notification of amounts due

When making payments, the JU 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 JU 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 JU 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: [redacted]
Full name of the account holder: KING S COLLEGE LONDON
IBAN code: [redacted]

21.9 Costs of payment transfers

The cost of the payment transfers is borne as follows:

- the JU 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 JU 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 JU 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 JU and the Commission

22.1.1 Right to carry out checks

The JU 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 JU may be assisted by external persons or bodies.

The JU may also request additional information in accordance with Article 17. The JU 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 JU may — during the implementation of the action or afterwards — carry out reviews on the proper implementation of the action (including assessment of deliverables and reports), compliance with the obligations under the Agreement and continued scientific or technological relevance of the action.

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

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

The JU 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 JU 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 JU 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 JU 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.

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

The JU 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 JU 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 JU 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 JU 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 JU 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[16] and No 2185/96[17] (and in accordance with their provisions and procedures), and Article 50 of the JU Financial Rules, 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.

[16] 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).

[17] 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).

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 50 of the JU Financial Rules, 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 JU, EU or Euratom grants awarded under similar conditions ('**extension of findings from this grant to other grants**').

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

22.5.2 Findings in other grants

The JU 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 JU, 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 JU 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 JU 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 JU or the Commission in justified cases.

The JU or the Commission may then start a rejection procedure in accordance with Article 42, on the basis of:

- the revised financial statements, if approved;
- the proposed alternative correction method, if accepted

or

- the initially notified correction rate for extrapolation, if it 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.

22.5.3.2 If the findings concern **substantial errors**, **irregularities or fraud** or **serious breach of obligations**: 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 JU 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.

The JU or the Commission may then start a reduction procedure in accordance with Article 43, on the basis of:

- the proposed alternative flat-rate, if accepted

or

- the initially notified flat-rate, if it does not receive any observations or does not accept the observations or the proposed 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 JU 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 JU 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 JU 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[19].

[19] 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.

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

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

23a.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the JU 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 (See Article 25.3 and Article 25.4).

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 24a — TRANSFER AND LICENSING OF BACKGROUND

Each beneficiary remains free to license, transfer or otherwise dispose of its ownership rights in background, subject to any rights and obligations under this Agreement and the consortium agreement.

Where a beneficiary transfers ownership of background, it must pass on its obligations specified under this Agreement and the consortium agreement, regarding that background, to the transferee, including the obligation to pass those obligations on to any subsequent transferee.

A beneficiary may, without the consent of the other beneficiaries but provided that the other beneficiaries are informed without undue delay and that the transferee agrees in writing to be bound by this Agreement and the consortium agreement, transfer its background to any of the following:

(a) its affiliated entity,

(b) any purchaser of all or a substantial amount of its relevant assets, and

(c) any successor entity resulting from the merger with or consolidation of such a beneficiary.

The delay referred to in the third subparagraph must be agreed by the beneficiaries in the consortium agreement.

ARTICLE 25 — ACCESS RIGHTS TO BACKGROUND

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

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

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

Waivers of access rights are not valid unless in writing.

Unless agreed otherwise, access rights do not include the right to sub-license. However, any legal entity that enjoys access rights in order to complete the action or for research use (see Article 25.3) may authorize another legal entity to exercise those rights on its behalf, provided that the following conditions are fulfilled:

(a) the legal entity that enjoys access rights is liable for the acts of the other legal entity as if those acts had been performed by this former legal entity;

(b) access rights granted to the other legal entity do not include the right to sub-license.

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

During the action, the beneficiaries enjoy (unless prevented or restricted from doing so by obligations to others, which exist at the date of accession to this Agreement) access rights to the background of the other beneficiaries, solely for the purpose and to the extent necessary for undertaking and completing the action.

Such access must be granted on a royalty-free basis.

25.3 Access rights for other beneficiaries and their affiliated entities, for exploiting results

The following definitions as regards exploitation shall apply:

(a) 'research use' means the use of results or background needed to use results, for all purposes other than for completing the action or for direct exploitation, and which includes but is not limited to the application of results as a tool for research, including clinical research and trials, and which directly or indirectly contributes to the objectives set out in the Societal Challenge health, demographic change and well-being referred to in Regulation (EU) No 1291/2013.

(b) 'direct exploitation' means developing results for commercialization, including through clinical trials, or commercializing results themselves.

During and after completion of the action, beneficiaries and their affiliated entities enjoy (unless prevented or restricted from doing so by obligations to others which exist at the date of accession to this Agreement) access rights to the background of the other beneficiaries, only to the extent reasonably required for the purpose of the research use of results.

Such access rights for research use must be granted on a non-exclusive basis under fair and reasonable

conditions (i.e. appropriate conditions, including financial terms or royalty-free, taking into account the actual or potential value of the background to which access is requested and other characteristics of the research use envisaged).

Beneficiaries are not required to grant access rights for direct exploitation to their own background and may use, exploit, sublicense or otherwise commercialize their background as they see fit, subject to access rights for research use.

Where direct exploitation by a beneficiary or third party, requires background necessary to use results owned by another beneficiary, the access rights may be negotiated between the parties involved.

Beneficiaries must agree in the consortium agreement on a time-limit in respect of requests for access.

25.4 Access rights for third parties

After completion of the action, (unless prevented or restricted from doing so by obligations to others which exist at the date of accession to this Agreement) third parties have the right to request and receive access rights to the background of the beneficiaries, only to the extent reasonably required for the purpose of the research use of results.
Such access rights must be granted on a non-exclusive basis, under conditions considered appropriate by the owner of the background and the third party concerned.

Before the signature of this Agreement or when identifying and agreeing on background (see Article 24) thereafter, a beneficiary may identify specific elements of the background and provide a reasoned request to the JU Programme office that such elements must be wholly or partially, excluded from the obligations referred to in the first subparagraph. The JU Programme office will only grant such request in exceptional circumstances and in making its decision will consider the objectives referred to in Article 2 of Regulation (EU) No 557/2014, the tasks of JU referred to in its statutes and the legitimate interests of the beneficiary concerned. It may grant such request on conditions agreed with the beneficiary. Any exceptions must be included in this Agreement and cannot be changed unless such change is permitted by this Agreement.

Beneficiaries must agree in the consortium agreement on a time-limit in respect of requests for access.

25.5 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 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.

Results do not include any sideground, defined as tangible or intangible output generated by a beneficiary under the action, such as data, knowledge and information whatever their form or nature, whether or not they can be protected, but which are outside of the action objectives as defined in this Agreement and which therefore are not needed for implementing the action or for research use of results.

Each beneficiary remains the exclusive owner of its sideground but a different allocation of ownership may be agreed upon in the consortium agreement.

Beneficiaries are not required to grant access rights to sideground.

26.2 Joint ownership by several beneficiaries

Two or more beneficiaries own results jointly if:

(a) they have jointly generated them and

(b) it is not possible to:

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

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

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

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

(a) at least 45 days advance notice and

(b) fair and reasonable compensation.

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

26.3 Rights of third parties (including personnel)

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

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

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

26.4 JU ownership, to protect results

26.4.1 The JU 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 JU 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 JU decides to assume ownership, it will formally notify the beneficiary concerned within 45 days of receiving notification.

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

26.4.2 The JU 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 JU 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 JU 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 any of the other measures described in Chapter 6.

ARTICLE 27 — PROTECTION OF RESULTS — VISIBILITY OF JU FUNDING AND SUPPORT FROM JU MEMBERS

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 JU 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 JU may — under certain conditions (see Article 26.4) — assume ownership to ensure their (continued) protection.

27.3 Information on JU funding and support from JU members and associated partners

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

> "The project leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777394. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and AUTISM SPEAKS, Autistica, SFARI.".

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.

In addition, the beneficiaries must — up to four years after the period set out in Article 3 — comply with the additional exploitation obligations set out in Annex 1.

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 JU funding and support from JU members and associated partners

If results are incorporated in a standard, the beneficiary concerned must — unless the JU 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 Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777394. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and AUTISM SPEAKS, Autistica, SFARI.".

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 JU FUNDING AND SUPPORT FROM JU MEMBERS

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).

In addition, the beneficiaries must comply with the additional dissemination obligations set out in Annex 1.

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 JU 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 "Innovative Medicines Initiative 2 Joint Undertaking", "European Union (EU)", "Horizon 2020" and “EFPIA” and “AUTISM SPEAKS”, “Autistica”, “SFARI”;
- 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

Regarding the digital research data generated in the action (‘**data**’), the beneficiaries must:

(a) deposit in a research data repository and take measures to make it possible for third parties to access, mine, exploit, reproduce and disseminate — free of charge for any user — the following:

(i) the data, including associated metadata, needed to validate the results presented in scientific publications as soon as possible;

(ii) not applicable;

(iii) other data, including associated metadata, as specified and within the deadlines laid down in the 'data management plan' (see Annex 1);

(b) provide information — via the repository — about tools and instruments at the disposal of the beneficiaries and necessary for validating the results (and — where possible — provide the tools and instruments themselves).

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.

As an exception, the beneficiaries do not have to ensure open access to specific parts of their research data under Point (a)(i) and (iii), if the achievement of the action's main objective(as described in Annex 1) would be jeopardised by making those specific parts of the research data openly accessible. In this case, the data management plan must contain the reasons for not giving access.

29.4 Information on JU funding and support from JU members and associated partners — Obligation and right to use the logos and the EU emblem

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

(a) display the JU logo, the logo of EFPIA and of AUTISM SPEAKS, Autistica, SFARI and

(b) display the EU emblem and

(c) include the following text:

> *"This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777394. The JU receives support from the European Union's Horizon 2020 research and innovation programme* and EFPIA and AUTISM SPEAKS, Autistica, SFARI*".*

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

For the purposes of their obligations under this Article, the beneficiaries may use the logos and emblem without first obtaining approval from the JU, the Commission or the JU Members and associated partners.

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

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

29.5 Disclaimer excluding JU responsibility

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

Notwithstanding the above, a beneficiary may, without the consent of the other beneficiaries but provided that the other beneficiaries are informed without undue delay and that the transferee agrees in writing to be bound by this agreement and the consortium agreement, transfer its results to any of the following:

(i) its affiliated entity;

(ii) any purchaser of all or a substantial amount of its relevant assets;

(iii) any successor entity resulting from the merger with or consolidation of such a beneficiary.

The delay referred to in the sixth subparagraph must be agreed by the beneficiaries in the consortium agreement.

30.2 Granting licenses

Provided that any access rights to the results can be exercised and that any additional obligations under this Agreement or consortium agreement are complied with by the beneficiary who owns results, the latter may grant licences to its results (or otherwise give the right to exploit them) to any legal entity.

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

30.3 JU right to object to transfers or licensing

The JU 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 JU 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 JU 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 JU may request additional information.

If the JU 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 JU decision, within the period set out above;
- if the JU objects;
- until the conditions are complied with, if the JU 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

During the action, beneficiaries enjoy access rights to the results of the other beneficiaries solely for the purpose and to the extent necessary for undertaking and completing the action.

Such access must be granted on a royalty-free basis.

31.3 Access rights for other beneficiaries and their affiliated entities, for exploiting results

During and after completion of the action, beneficiaries and their affiliated entities enjoy access rights to the results of the other beneficiaries for research use (see Article 25.3).

Access rights for research use must be granted on a non-exclusive basis under fair and reasonable conditions (i.e. appropriate conditions including financial terms or royalty-free, taking into account

the actual or potential value of the results to which access is requested and other characteristics of the research use envisaged).

Where direct exploitation by a beneficiary or third party requires results owned by another beneficiary, the access rights may be negotiated between the parties involved.

Beneficiaries must agree in the consortium agreement on a time-limit in respect of requests for access.

31.4 Access rights of affiliated entities

Not applicable

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

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

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

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

31.6 Access rights for third parties

After the completion of the action, third parties shall have the right to request and receive access rights to the results of the beneficiaries for research use.

Such access rights must be granted on a non-exclusive basis under conditions considered appropriate by the owner of the results and the third party concerned. Those conditions may not be more favorable than the conditions applied to beneficiaries and affiliated entities for research use.

Beneficiaries must agree in the consortium agreement on a time-limit in respect of requests for access.

31.7 Consequences of non-compliance

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

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

SECTION 4 OTHER RIGHTS AND OBLIGATIONS

ARTICLE 32 — RECRUITMENT AND WORKING CONDITIONS FOR RESEARCHERS

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

The beneficiaries must take all measures to implement the principles set out in the Commission

Recommendation on the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers[21], in particular regarding:

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

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

32.2 Consequences of non-compliance

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

ARTICLE 33 — GENDER EQUALITY

33.1 Obligation to aim for gender equality

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

33.2 Consequences of non-compliance

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

ARTICLE 34 — ETHICS AND RESEARCH INTEGRITY

34.1 Obligation to comply with ethical and research integrity principles

The beneficiaries must carry out the action in compliance with:

(a) ethical principles (including the highest standards of research integrity)

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 or for activities which destroy human embryos (for example, for obtaining stem cells).

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:

[21] 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).

(a) aim at human cloning for reproductive purposes;

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

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

In addition, the beneficiaries must respect the fundamental principle of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity[22].

This implies compliance with the following fundamental principles:

- **reliability** in ensuring the quality of research reflected in the design, the methodology, the analysis and the use of resources;

- **honesty** in developing, undertaking, reviewing, reporting and communicating research in a transparent, fair and unbiased way;

- **respect** for colleagues, research participants, society, ecosystems, cultural heritage and the environment;

- **accountability** for the research from idea to publication, for its management and organisation, for training, supervision and mentoring, and for its wider impacts

and means that beneficiaries must ensure that persons carrying out research tasks follow the good research practices and refrain from the research integrity violations described in this Code.

This does not change the other obligations under this Agreement or obligations under applicable international, EU or national law, all of which still apply.

34.2 Activities raising ethical issues

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

Before the beginning of an activity raising an ethical issue, each beneficiary must have obtained:

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

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

needed for implementing the action tasks in question.

The documents must be kept on file and be submitted upon request by the coordinator to the JU (see Article 52). If they are not in English, they must be submitted together with an English summary, which shows that the action tasks in question are covered and includes the conclusions of the committee or authority concerned (if available).

[22] European Code of Conduct for Research Integrity of ALLEA (All European Academies) http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/h2020-ethics_code-of-conduct_en.pdf

34.3 Activities involving human embryos or human embryonic stem cells

Activities involving research on human embryos or human embryonic stem cells may be carried out, in addition to Article 34.1, only if:

- they are set out in Annex 1 or
- the coordinator has obtained explicit approval (in writing) from the JU (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 JU 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 JU 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 JU may agree to keep such information confidential for an additional period beyond the initial four years.

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

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

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

(a) need to know to implement the Agreement and

(b) are bound by an obligation of confidentiality.

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

The JU may disclose confidential information to its staff, other EU institutions and bodies. It may disclose confidential information to third parties, if:

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

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

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 information

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 JU FUNDING AND SUPPORT FROM JU MEMBERS

38.1 Communication activities by beneficiaries

38.1.1 Obligation to promote the action and its results

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

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

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

38.1.2 Information on JU funding and support from JU members and associated partners — Obligation and right to use the logos and the EU emblem

Unless the JU 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 JU logo, the logo of EFPIA and of and AUTISM SPEAKS, Autistica, SFARI and

(b) display the EU emblem and

(c) include the following text:

For communication activities:

"This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777394. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and AUTISM SPEAKS, Autistica, SFARI".

For infrastructure, equipment and major results:

"This *[infrastructure][equipment][insert type of result]* is part of a project that has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777394. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and AUTISM SPEAKS, Autistica, SFARI".

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

For the purposes of their obligations under this Article, the beneficiaries may use the logos and the EU emblem without first obtaining approval from the JU, the Commission or the JU Members and AUTISM SPEAKS, Autistica, SFARI.

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

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

38.1.3 Disclaimer excluding JU responsibility

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

38.2 Communication activities by the JU

38.2.1 Right to use beneficiaries' materials, documents or information

The JU 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 received 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.

If the JU's use of these materials, documents or information would risk compromising legitimate interests, the beneficiary concerned may request the JU 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 JU or any other EU institution, body, office or agency or body or institutions in EU Member States; and copying or reproducing them in whole or in part, in unlimited numbers);

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

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

(d) translation;

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

(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

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

in Points (b), (c), (d) and (f) to third parties if needed for the communication and publicising activities of the JU.

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 JU will insert the following information:

"© – [year] – [name of the copyright owner]. All rights reserved. Licensed to the Innovative Medicines Initiative 2 Joint Undertaking under conditions."

38.3 Consequences of non-compliance

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

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

ARTICLE 39 — PROCESSING OF PERSONAL DATA

39.1 Processing of personal data by the JU and the Commission

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

Such data will be processed by the '**data controller**' of the JU or the Commission for the purposes of implementing, managing and monitoring the Agreement or protecting the financial interests of the JU, 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 privacy statement(s) that are published on the JU 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

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

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

39.3 Consequences of non-compliance

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

ARTICLE 40 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE JU

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

If the JU 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 JU.

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 JU

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 JU funding for doing so), unless the JU expressly relieves them of this obligation.

The **financial responsibility** of each beneficiary is governed by Articles 44.

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 Participant Portal 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 its linked third parties 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 JU under the Agreement, unless the Agreement requires the beneficiary to submit this information directly to the JU.

(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 JU (in particular, providing the JU with the information described in Article 17), unless the Agreement specifies otherwise;

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

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

The coordinator may not delegate or subcontract the above-mentioned tasks to any other beneficiary or third party (including linked third parties).

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, including allocation of scientific tasks among beneficiaries;
- management of access to the electronic exchange system;
- distribution of JU 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 — SANCTIONS — DAMAGES — SUSPENSION — TERMINATION — FORCE MAJEURE

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

ARTICLE 42 — REJECTION OF INELIGIBLE COSTS

42.1 Conditions

The JU will — after **termination of the participation of a beneficiary**, 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).

The rejection may also be based on the **extension of findings from other grants to this grant** (see Article 22.5.2).

42.2 Ineligible costs to be rejected — Calculation — Procedure

Ineligible costs will be rejected in full.

If the rejection of costs does not lead to a recovery (see Article 44), the JU will formally notify the coordinator or beneficiary concerned of 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 JU of its disagreement and the reasons why.

If the rejection of costs leads to a recovery, the JU will follow the contradictory procedure with pre-information letter set out in Article 44.

42.3 Effects

If the JU 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 JU rejects costs **after termination of the participation of a beneficiary**, it will deduct them from the costs declared by the beneficiary in the termination report and include the rejection in the calculation after termination (see Article 50.2 and 50.3).

If the JU — **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 JU 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

The JU may — **after termination of the participation of a beneficiary**, **at the payment of the balance** or **afterwards** — reduce the grant amount (see Article 5.1), if :

(a) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed:

  (i) substantial errors, irregularities or fraud or

  (ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles) or

(b) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) 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).

43.2 Amount to be reduced — Calculation — Procedure

The amount of the reduction will be proportionate to the seriousness of the errors, irregularities or fraud or breach of obligations.

Before reduction of the grant, the JU 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 JU 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 JU reduces the grant **after termination of the participation of a beneficiary**, it will calculate the reduced grant amount for that beneficiary and then determine the amount due to that beneficiary (see Article 50.2 and 50.3).

If the JU reduces the grant **at 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 JU 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 JU will recover the difference (see Article 44).

ARTICLE 44 — RECOVERY OF UNDUE AMOUNTS

44.1 Amount to be recovered — Calculation — Procedure

The JU 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 (including undue amounts paid by the JU for costs declared by its linked third parties), 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 JU 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 JU will **recover** the amount:

(a) by '**offsetting**' it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the JU.

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

(b) if a linked third party has accepted joint and several liability (see Article 14), by **holding the third party liable** up to the maximum JU contribution indicated, for the linked third party, in the estimated budget (see Annex 2) and/or

(c) by **taking legal action** (see Article 57).

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 JU receives full payment of the amount.

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

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

44.1.2 Recovery at payment of the balance

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

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

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

If the coordinator does not repay the JU by the date in the debit note, but has submitted the report on the distribution of payments: the JU 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 JU multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned

plus

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

its linked third parties' costs declared in the final summary financial statement and approved by the JU multiplied by the reimbursement rate set out in Article 5.2 for each linked third party concerned}

divided by

the JU 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 JU will **recover** the amount:

(a) by **offsetting** it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the JU.

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

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

(i) if a linked third party has accepted joint and several liability (see Article 14), by **holding the third party liable** up to the maximum JU contribution indicated, for the linked third party, in the estimated budget (see Annex 2) and/or

(ii) by **taking legal action** (see Article 57).

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 JU 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 JU.

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 JU multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned

plus

its linked third parties' costs declared in the final summary financial statement and approved by the JU multiplied by the reimbursement rate set out in Article 5.2 for each linked third party concerned}

divided by

the JU 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 JU will also recover these amounts.

The JU 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 JU 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 JU will **recover** the amount:

(a) by **offsetting** it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the JU.

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

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

(i) if a linked third party has accepted joint and several liability (see Article 14), by **holding the third party liable** up to the maximum JU contribution indicated, for the linked third party, in the estimated budget (see Annex 2) and/or

(ii) by **taking legal action** (see Article 57).

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 JU 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 SANCTIONS

In addition to contractual measures, the JU may also adopt administrative sanctions under Articles 33 and 35 of the JU Financial Rules read in conjunction with Articles 106 and 131(4) of the Financial Regulation No 966/2012 (i.e. exclusion from future procurement contracts, grants, prizes and expert contracts and/or financial penalties).

SECTION 2 LIABILITY FOR DAMAGES

ARTICLE 46 — LIABILITY FOR DAMAGES

46.1 Liability of the JU

The JU 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 JU 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

Except in case of force majeure (see Article 51), the beneficiaries must compensate the JU 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.

SECTION 3 SUSPENSION AND TERMINATION

ARTICLE 47 — SUSPENSION OF PAYMENT DEADLINE

47.1 Conditions

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

The suspension will **take effect** the day notification is sent by the JU (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 JU 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 JU 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 JU may — at any moment — suspend payments, in whole or in part and for one or more beneficiaries, if:

(a) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed or is suspected of having committed:

  (i) substantial errors, irregularities or fraud or

  (ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles) or

(b) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed — in other JU, 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).

If payments are suspended for one or more beneficiaries, the JU will make partial payment(s) for the part(s) not suspended. If suspension concerns the payment of the balance, — once suspension is lifted — the payment or the recovery of the amount(s) concerned will be considered the payment of the balance that closes the action.

48.2 Procedure

Before suspending payments, the JU will formally notify the coordinator or beneficiary concerned:

- 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 JU 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 JU.

If the conditions for resuming payments are met, the suspension will be **lifted**. The JU will formally notify the coordinator or beneficiary concerned.

During the suspension, the periodic report(s) for all reporting periods except the last one (see Article 20.3), must not contain any individual financial statements from the beneficiary concerned and its linked third parties. The coordinator must include them in the next periodic report after the suspension is lifted or — if suspension is not lifted before the end of the action — in the last 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 JU 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 JU.

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

49.2.1 Conditions

The JU may suspend implementation of the action or any part of it, if:

(a) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed or is suspected of having committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles);

(b) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed — in other JU, 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) the action is suspected of having lost its scientific or technological relevance.

49.2.2 Procedure

Before suspending implementation of the action, the JU will formally notify the coordinator or beneficiary concerned:

- 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 JU 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 (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 or beneficiary concerned 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 JU (see Article 46).

Suspension of the action implementation does not affect the JU'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 JU (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 JU 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 JU 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 JU 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, 40, 42, 43 and 44) 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 JU (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 JU 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 JU, (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 JU, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The JU will — on the basis of the periodic reports, the termination report and the report on the distribution of payments — **calculate** the amount which is due to the beneficiary and if the (pre-financing and interim) payments received by the beneficiary exceed this amount.

The **amount which is due** is calculated in the following steps:

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

The grant amount for the beneficiary is calculated by applying the reimbursement

rate(s) to the total eligible costs declared by the beneficiary and its linked third parties in the termination report and approved by the JU.

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.

Step 2 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

In case of a reduction (see Article 43), the JU will calculate the reduced grant amount for the beneficiary by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the grant amount for the beneficiary.

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 JU 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 JU 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 JU 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 JU the amount due and the JU 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 JU 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 JU the amount due. The JU 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 JU 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 JU 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, 40, 42, 43 and 44) continue to apply.

50.3 Termination of the Agreement or the participation of one or more beneficiaries, by the JU

50.3.1 Conditions

The JU 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 (or those of its linked third parties) 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;

(l) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles);

(m) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed — in other JU, 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).

(n) despite a specific request by the JU, a beneficiary does not request — through the coordinator — an amendment to the Agreement to end the participation of one of its linked third parties or international partners that is in one of the situations under points (e), (f), (g), (k), (l) or (m) and to reallocate its tasks.

50.3.2 Procedure

Before terminating the Agreement or participation of one or more beneficiaries, the JU will formally notify the coordinator or beneficiary concerned:

- 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 JU of the measures to ensure compliance with the obligations under the Agreement.

If the JU does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify to the coordinator or beneficiary concerned **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), (l.ii) and (n) 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.

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 reports (see Articles 20.8 and 50.3.1(l)), the coordinator may not submit any reports after termination.

If the JU 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 JU 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 JU's right to reduce the grant (see Article 43) or to impose administrative sanctions (Article 45).

The beneficiaries may not claim damages due to termination by the JU (see Article 46).

After termination, the beneficiaries' obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) 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 JU, (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 JU, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The JU will — on the basis of the periodic reports, the termination report and the report on the distribution of payments — **calculate** the amount which is due to the beneficiary and if the (pre-financing and interim) payments received by the beneficiary exceed this amount.

The **amount which is due** is calculated in the following steps:

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

The grant amount for the beneficiary is calculated by applying the reimbursement rate(s) to the total eligible costs declared by the beneficiary and its linked third parties in the termination report and approved by the JU.

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.

Step 2 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

In case of a reduction (see Article 43), the JU will calculate the reduced grant amount for the beneficiary by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the grant amount for the beneficiary.

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 JU 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 JU 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 JU 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 JU the amount due and the JU 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 JU 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

JU the amount due. The JU 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 JU 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 JU 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, 40, 42, 43 and 44) continue to apply.

SECTION 4 FORCE MAJEURE

ARTICLE 51 — FORCE MAJEURE

'Force majeure' means any situation or event that:

- prevents either party from fulfilling their obligations under the Agreement,
- was unforeseeable, exceptional situation and beyond the parties' control,
- was not due to error or negligence on their part (or on the part of third parties involved in the action), and
- proves to be inevitable in spite of exercising all due diligence.

The following cannot be invoked as force majeure:

- any default of a service, defect in equipment or material or delays in making them available, unless they stem directly from a relevant case of force majeure,
- labour disputes or strikes, or
- financial difficulties.

Any situation constituting force majeure must be formally notified to the other party without delay, stating the nature, likely duration and foreseeable effects.

The parties must immediately take all the necessary steps to limit any damage due to force majeure and do their best to resume implementation of the action as soon as possible.

The party prevented by force majeure from fulfilling its obligations under the Agreement cannot be considered in breach of them.

CHAPTER 7 FINAL PROVISIONS

ARTICLE 52 — COMMUNICATION BETWEEN THE PARTIES

52.1 Form and means of communication

Communication under the Agreement (information, requests, submissions, 'formal notifications', etc.) must:

- be made in writing and
- bear the number of the Agreement.

All communication must be made through the Participant Portal **electronic** exchange system and using the forms and templates provided there.

If — after the payment of the balance — the JU finds that a formal notification was not accessed, a second formal notification will be made by registered post with proof of delivery ('formal notification on **paper**'). Deadlines will be calculated from the moment of the second notification.

Communications in the electronic exchange system must be made by persons authorised according to the Participant Portal Terms & Conditions. 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 Participant Portal Terms & Conditions).

If the electronic exchange system is temporarily unavailable, instructions will be given on the JU 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 JU 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 JU** must be sent to the official mailing address indicated on the JU's website.

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 Participant Portal Beneficiary Register.

ARTICLE 53 — INTERPRETATION OF THE AGREEMENT

53.1 Precedence of the Terms and Conditions over the Annexes

The provisions in the Terms and Conditions of the Agreement take precedence over its Annexes.

Annex 2 takes precedence over Annex 1.

53.2 Privileges and immunities

Not applicable

ARTICLE 54 — CALCULATION OF PERIODS, DATES AND DEADLINES

In accordance with Regulation No 1182/71[28], periods expressed in days, months or years are calculated from the moment the triggering event occurs.

The day during which that event occurs is not considered as falling within the period.

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).

[28] Regulation (EEC, Euratom) No 1182/71 of the Council of 3 June 1971 determining the rules applicable to periods, dates and time-limits (OJ L 124, 8.6.1971, p. 1).

The request for amendment must include:

- the reasons why;
- the appropriate supporting documents, and
- for a change of coordinator without its agreement: the opinion of the coordinator (or proof that this opinion has been requested in writing).

The JU 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 JU 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) and for beneficiaries for which the JU has requested joint and several liability of a linked third party, by also submitting — at accession — a declaration on joint and several liability (see Annex 3a) signed by the third party.

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 JU'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).

As an exception, if such a dispute is between the JU and F. HOFFMANN-LA ROCHE AG, UNIVERSITAT BASEL, STELLENBOSCH UNIVERSITY, NOVARTIS PHARMA AG, TEVA PHARMACEUTICAL INDUSTRIES LIMITED, AUTISM SPEAKS INC. NON PROFIT CORPORATION, THE SIMONS FOUNDATION, INC, the competent Belgian courts have sole jurisdiction.

If a dispute concerns administrative sanctions or offsetting, the beneficiaries must bring action before the General Court — or, on appeal, the Court of Justice of the European Union — under Article 263 TFEU.

ARTICLE 58 — ENTRY INTO FORCE OF THE AGREEMENT

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

SIGNATURES

For the coordinator

[redacted]

For the JU

Signed by Pierre MEULIEN [redacted]

Work package number [9]	WP7	Lead beneficiary [10]	1 - KCL
Work package title	Ethics requirements		
Start month	1	End month	60

Objectives

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

Description of work and role of partners

WP7 - Ethics requirements [Months: 1-60]
KCL
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]
D7.1	GEN - Requirement No. 11	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D7.2	GEN - Requirement No. 12	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	18
D7.3	GEN - Requirement No. 13	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	60
D7.4	GEN - Requirement No. 14	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.5	GEN - Requirement No. 15	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	24
D7.6	GEN - Requirement No. 16	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	36

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D7.7	GEN - Requirement No. 17	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	48
D7.8	GEN - Requirement No. 18	1 - KCL	Ethics	Confidential, only for members of the consortium (including the Commission Services)	60

Description of deliverables

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

D7.1 : GEN - Requirement No. 11 [6]

An internal register to keep track of necessary approvals of ethics committees and competent authorities and their status is established

D7.2 : GEN - Requirement No. 12 [18]

updated mid term of the internal register to keep track of necessary approvals of ethics committees and competent authorities and their status

D7.3 : GEN - Requirement No. 13 [60]

Final version of the internal ethics register

D7.4 : GEN - Requirement No. 14 [12]

Report from the ethics board and ethics advisor

D7.5 : GEN - Requirement No. 15 [24]

Report from the ethics board and ethics advisor

D7.6 : GEN - Requirement No. 16 [36]

Report from the ethics board and ethics advisor

D7.7 : GEN - Requirement No. 17 [48]

Report from the ethics board and ethics advisor

D7.8 : GEN - Requirement No. 18 [60]

Report from the ethics board and ethics advisor

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification

5 Ethics and Security

5.1 Ethics

OVERALL ISSUES AND APPROACHES

We are very much aware that our proposal involves complex issues, and that new information may become available during the course of our studies that have ethical implications. Hence, we have included an independent Ethics Advisory Board. Professor [redacted], has kindly agreed to lead this aspect of our work. Through regular (quarterly) meetings, the Ethics Board will ensure that our ethical approaches are consistent across work packages and across countries wherever appropriate; provide expert advice to the rest of the consortium on any specific ethical issues arising in particular studies; engage key experts to provide additional advice where necessary (e.g. new EU legislation as it arises); and develop strategies to explore the ethical implications of novel results as they emerge from the consortium (see below). Professor [redacted] will ensure that the Ethics Board includes relevant independent expertise to monitor the ethics issues in this project and how they are handled. The Board will be consulted at least on the following points (inclusion of fetuses, infants at risk, imaging, animal models, genetic information, dedication, clinical trials and data protection). A report by the Ethics Board will be submitted as a deliverable at the end of each reporting period.

Any consideration of ethical issues has to be set in a context of the potential benefits and risks of the overall project. Undoubtedly, better options are needed for treating ASD. AIMS-2-TRIALS will address this issue using the latest techniques of animal and cellular models, genetics, proteomics, imaging and behavioural/cognitive phenotyping.

In pursuit of these objectives the ethical aspects to be addressed with respect to our proposal concern experiments using small laboratory animals (mice and rats, WP2) and investigations of human stem cells (WP2). To be clear our project does make stem cells derived from scalp hair (keratinocytes) or fibroblasts or existing human embryonic stem cell lines – but not new tissue from embryos. In the case of animal studies of AIMS-2-TRIALS we need to address the issues of necessity of animal experimentation and the choice of lowest species, the refinement of methods and the expertise of the individuals involved in handling, the reduction of animal use - insofar as possible with an eventual goal of replacement.

In this section we lay out a set of general principles which guide our overall approach in AIMS-2-TRIALS across both our human and 'basic' research, and we then address the individual issues is separate sections (e.g. in humans and animals).

Overall principles impacting on all our studies.

- The participating investigators of AIMS-2-TRIALS agree to adhere to all relevant international, IMI and national legislation and guidelines relating to the conduct of all our studies.
- All research activities within AIMS-2-TRIALS requiring approval on ethical and legal grounds through responsible local or national Ethics Committees and Regulatory Authorities will be conducted only after obtaining approval.
- AIMS-2-TRIALS will comply with the highest ethical standards, including those outlined in the Grant Agreement (Article 34 of the Model Grant Agreement) and the European Code of Conduct for Research integrity. The balance between the research objectives and the means used to achieve them will be given special attention.
- Most of the experimentation is being conducted in EU countries. However some work packages, e.g. WP2,3,4,and 6, which will also share some data from South African (SPS), Canadian (POND), US (ABC-CT), and Australian (CRC) sources). These will be subject to appropriate EU regulations and supplementary local regulations where appropriate. Also we will ensure that the research conducted outside the EU is legal in at least one member state.
- The experiments and studies are all being led by investigators who have established (usually two decades) of track record of excellent scientific work in their respective areas – thus assuring scientific expertise, established infrastructure and experience within the local regulatory authorities with the kind of work being proposed.
- While AIMS-2-TRIALS will use an array of procedures, genetic and other metabalomic analysis (and the specific ethical issues are addressed below), we are not introducing any radically new first-in-man procedures nor are we introducing any incrementally invasive techniques in animals.
- However where we do carry out animal experiments the anticipated benefits of the project justify their use due to the fact that alternative methods are not applicable. The 3 Rs rule (i.e. Replace, Reduce, Refine) will be strictly applied.
-

Overall principles impacting mainly on human studies. In addition to the general principles described above, our foremost principles for the conduct of any research involving human participants within AIMS-2-TRIALS are:

- Respect for the rights, integrity and privacy of patients
- Protection of vulnerable patients
- Continuous monitoring of patients' safety
- Generation of meaningful, high-quality data

- Timely publication of results
- A comprehensive policy for incidental findings.
- Clarity with participants that they can leave the study at any time with no deleterious consequences

Moreover research in AIMS-2-TRIALS involving human participants will be conducted under the applicable international, IMI and national laws and regulations. This also applies when collecting, obtaining, or using any samples for research

In particular, the consortium is committed to

- The DECLARATION OF HELSINKI: Ethical Principles for Medical Research Involving Human Subjects (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013)
- The standards of the International Conference on Harmonisation (ICH) / Good Clinical Practice (GCP)
- The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, ETS No. 164, Oviedo, 4 April 1997; and the Additional Protocol on Biomedical Research (CETS No. 195), 2005. And the UNESCO: Universal Declaration on Bioethics and Human Rights (2005).
- Submitting copies of ethical approvals by the competent legal local/national Ethics Boards/Bodies to the IMI prior to the commencement of research.
- Being explicit in the Informed Consent Forms that data can be used in the future for research and commercial purposes.

Human issues. An overview

Our in vivo research with humans includes; 1) healthy volunteers (WP2), 2) phenotyping research with fetuses, infants, children, adolescents, and adults with and without ASD (WP2) that includes imaging studies (WP2).; 3) experiments (in adults only) that use pharmacological probes (WP3) to explore causes of brain dysfunction, and ionising radiation (PET) to explore specific neurochemical systems, 4) clinical trials using drugs (WPs 3-4), 5) the use of human biological samples and the collection of human data, and research involving processing and analysis of genetic information or phenotypic or personal data (WPs 2,3,4,6). We already have local and national ethics approval for our work with fetuses, infants, older children and adults (age > 6 years) and at KCL for children age 3-6 and for the pharmacological probe studies in those > 18 years). However, at other sites we will need to obtain ethics for our studies of 3-6 year olds (WP2), for studies of brain response to pharmacological probes (WP2) in adults, and for clinical trials (WP3 and 4) in children and adolescents/young adults. No clinical trials are proposed in any individuals who are less than 55 years of age, and no pharmaco-probe studies on brain function are planned in any individuals who are less than 18 years of age.

The human studies in AIMS-2-TRIALS raise a number of additional issues. These include the appropriateness of design of the studies, the expertise of the investigators carrying it out, the rigour of the local approval process and their ability to assess the balance risk and benefits, the validity of the informed consent procedure, the efforts to minimize any risks to volunteers/patients, protection of data and privacy and mechanisms for monitoring as well as sensitive mechanisms of response if things go wrong. For instance, major ethical siderationconsideration will be the collection of potentially sensitive data relating to health and specifically mental health, and the process of active and passive remote monitoring. We have described within section 5.1.4 steps taken to protect privacy, including deidentification of data, data security and training of all research workers in their duty to confidentiality. Any threats to privacy and all procedures for handling data will be explained to participants within the informed consent process.

Research with human participants will be conducted in the countries listed below in accordance with national and international regulations: UK, Ireland, Portugal, Spain, France, Italy, Netherlands, Belgium, Sweden, Germany, and South Africa.

Human issues. Shared themes impacting on recruitment/inclusion of subjects across all/most work packages

Our work packages involve the recruitment, assessment and follow up of patients with ASD and therefore demands the highest ethical standards. Key issues include competency to give written, informed consent, possible deficits in everyday concentration and attention, and fatigue and possible distress in the test situation. These studies will be conducted within 55 years across our clinical sites. In all cases the general (Helsinki and Madrid declarations) and the EU and local regulations regarding ethical conduct of human clinical trials will be followed. In specific, no patient legally detained under mental health legislation will be approached. Potential eligible subjects will be identified by advertisement and by clinical teams made aware of inclusion criteria. Such subjects, and/or their parents, will be approached by the research assistant with permission from the responsible medical officer, who will also be asked to confirm that the patient is competent to give informed consent, and that they are clinically stable. Some individuals we approach to take part in the study will have reduced capacity to give informed consent (e.g. those with intellectual disability). For details on our consent procedure please see below.

Human Issues. Consent

Subjects will be contacted by the research assistant and, in conjunction with a verbal explanation, provided with a written information sheet approved by national and local research ethics committees (the ethics review process in now a national Integrated Research Application System [IRAS] system in the UK). This will include the purpose of the study, why the person has been invited to take part, details of what they will be asked to do, how the data from the study will be kept secure and confidential in an appropriately pseudoanomised way, with identifiers removed, and assurance that participation or non-participation will not affect their clinical care. The information sheet will be left with the patient and/or their carer who will then be re-approached at their convenience to discuss any further questions and patients (and or their parent/carer in the case of children) who elect to participate will then provide written consent witnessed by a third party, usually a member of the clinical team.

Some recruited participants (i.e. fetuses, infants and children) will be under the age of consent, therefore informed consent will be obtained from the parents or guardians. Prior to obtaining consent, volunteers and their parents will have received an information sheet detailing all aspects of the study, including aims, methodology and benefits. Alternate information sheets using simplified language and images will be used for participants whose estimated developmental level is of an older child/younger adolescent, e.g. between 8 and 14 years. The study will be explained in detail to parents and guardians during telephone screening and on the screening visit. Assent will be sought from young people under the legal age for consent. At all points throughout recruitment and the study, participants and their parents will be encouraged to ask questions and air any concerns that may help clarify their role as a participant. For imaging studies of the fetus and newborn infants parents will be consented in the imaging centre, having been shown the MRI scanner and having had information, given to them, in some cases for some weeks prior. They will already have been in contact with the team to ask questions beforehand and on the day of scanning any remaining details of procedures involved are fully explained to them. All volunteers will be continually reminded that participation in the study is voluntary and that they are free to withdraw at any time. Participants and their families will be given a copy of the information sheet and signed consent form to keep.

The ethical approval from the relevant Local and/or National Research Ethics Service (NRES/HRA) that will be obtained before recruitment starts will contain explicit reference to the longitudinal follow up, and the possibility of the subjects being invited to participate in voluntary long-term follow up. There are a number of issues here:

- Follow up, as all research participation is voluntary and subjects can withdraw at any stage; this will be explicit in the patient information literature and the consent process. That is it will be made explicit that their consent is for the current contact/assessments and that they can then in future (when re-approached for follow up) again make an independent decision as to whether to continue to consent and/or withdraw (including withdrawal of retrospective data).
- The ethical permission granted before patient recruitment begins will include the taking of explicit consent for researchers to contact subjects or their families again in the long-term to invite their further participation.
- A related issue is the fact that even if subjects are not followed up long-term in the flesh, the images and DNA obtained will be used for many years, and there is a question about whether individuals should be asked for re-consent when they reach the age of majority for the use of their data and materials. We have taken advice on this from the Health Research Authority, which is the new national oversight body for all medical research. The Director, Professor [redacted], has given the opinion that in UK law consent for long-term follow up given by parents is adequate and appropriate for the long-term use of the materials, and that research could legally and ethically continue in the long term unless individuals asked for their materials to be destroyed. The right and process for this- which is ethically equivalent to voluntary withdrawal from the study- will be codified in the permissions granted by NRES before studies commence

Human issues. Determining capacity

Our study will use a similar protocol to assess capacity, and the same capacity assessment tool, as developed by KCL and approved by UK ethical review bodies (for use in an NIHR programme grant (ref. 09/H0807/72)). We are already using approach in EU AIMS.

Participants who are aged 16 or over. Following the protocol set out by project ref. 09/H0807/72, the initial step in determining who requires a capacity assessment will be to approach the consultant psychiatrist or physician in charge of the patient's treatment. Where the view of this person is expressly that the person has capacity to consent, no further assessment is appropriate or necessary as is standard practice (as stated in the Mental Capacity Act, 2005: "a person must be assumed to have capacity unless it is established that he lacks capacity). Where capacity is in doubt, it will be further assessed by an appropriately trained member of the treating team, together with a member of the research team. We are aware the baseline position is that capacity to consent is assumed unless there is reason to suppose otherwise. However, some neurological, psychological and/or behavioural markers may suggest lack of capacity for some things at some times. We also recognise that capacity is fluid in time and with respect to subject.

Given the nature of the research, it is clear that some people who may be eligible to participate may lack capacity. In this situation, the views of senior medical / psychology staff with regard to possible absence of capacity will be sought. Indicators of potential lack of capacity include (but are not restricted to) the diagnosis of learning disability (i.e. mental retardation), significant deficits in adaptive functioning or other signs or symptoms of mental disorder that might compromise capacity to give informed consent.

Where it is considered necessary by the clinical team that capacity should be assessed, the capacity assessment tool will be used to address the following questions, which are based upon the principles outlined in section 3(1) of the UK Mental Capacity Act, 2005:

- Can the person understand the information relevant to the decision?
- Can the person retain that information?
- Can the person use or weigh that information as part of the process of making the decision?
- Can the person communicate his/her decision (whether by talking, using sign language or any other means)?

Where it is identified that the participant may lack capacity to consent, the study will be introduced using the Participant Information Sheet (Easy read version) (Appendix S**).** Participants will be asked if they have any questions about the information they have been given. They will then be asked the questions on the Capacity Assessment form as part of the test of capacity (Appendix T: Mental Capacity Assessment ASD).

In the case that their child may lack capacity to consent, the letter to the parent asks them to nominate another relative or close family friend (other than themselves) to act as their son/daughter's personal consultee. The nominated personal consultee will be given the Personal Consultee General Information Sheet (see Appendix U) explaining what it means to be personal consultee and the Personal Consultee Signature Form ASD (Appendix V). We will try to arrange for the consultee and informant to be independent (i.e. one parent acts as the consultee, the other as the informantIf there are any concerns about a conflict of interest then the parent will be asked to contact the research team, at which stage we will speak to them about the possibility of finding an alternative personal consultee.

Participants recruited from child clinics/charities. Where the participant has been identified by referral from child clinics or from charities, if in the researchers' initial telephone conversation with the family, or the clinic, they identify that the son/daughter is aged 16 or older and may lack mental capacity to consent to participate in the research due to a diagnosis of learning disability, or significant deficits in adaptive functioning or other signs or symptoms of mental disorder that might compromise capacity to give informed consent, after appropriate training the researchers will arrange to assess the participant's mental capacity using the amended assessment of capacity to give informed consent. As above we will introduce the study using the Participant Information Sheet (Easy read version) before assessing capacity using the Capacity Assessment form. The personal consultee will be appointed using the same procedures as outlined above.

All researchers in our network will receive training from KCL, under the guidance of our ethics committee, in assessing mental capacity to consent. In addition, given that they may have to assess capacity without a clinician being present they will also undertake additional training: Mental Health Act 2005 (or European equivalents) and DOLS Awareness Training and Training on the Protection of Vulnerable Adults/Children training (POVA/POCA). Where possible, the researchers will conduct assessments in collaboration with a member of the healthcare team, known to the potential participant, with experience in assessing mental capacity. Moreover, where possible decisions will be made in collaboration between the research team and mental health team.

Human issues. Distress and fatigue

For participants with ASD, much of the distress around research involvement relates to new surroundings and new tasks. With this in mind, a booklet using words and images describing the research environment and investigations will be given to participants at least several days before the research assessment. Testing will take place at the participant's convenience either at home or in a research institute. Each session can take up to four hours and, in the case of participant fatigue, can be split over two consecutive days. In the event of a study participant becoming fatigued or distressed the following course of action will be taken: The cause of fatigue or distress will be established and discussed if participant wishes. The researcher, in collaboration with the participant and their carer will decide whether to proceed with the interview, re-schedule or continue with inclusion in the study. The participant will be free to withdraw from the study at any time. Participants will be reimbursed for any financial expenses incurred and will be paid 10 Euros or equivalent for each hour of assessment time. Children receive vouchers for books/educational toys in EU countries in which that is allowed. **We have successfully used protocols of this type and length across many hundreds of mothers, infants, children and adults with excellent acceptance and satisfaction. Moreover we** frequently carry out post-visit questionnaires to inform future protocols.

Human issues. Pregnancy

Pregnant and breast-feeding women will be included in our non interventional studies – but will not be included in any studies involving exposure to drugs or ionizing radiation.

Human issues. Filing copies of ethics approval(s).

Copies of opinions/approvals by ethics committees and/or competent authorities for the research with humans will be kept on file (and will be specified in the grant agreement).

Human issues. Cells/tissues – documenting procedures.

In case of the use of human cells/tissues obtained commercially, within the project, from another project, or obtained from a biobank, details on the cell/tissue types and on the biobank and access to it will be it kept on file (and this will be specified in the grant agreement). Moreover, copies of relevant documents for using, producing or collecting human cells or tissues (e.g., ethics approval, import licence, accreditation/designation/authorisation/licensing) will be kept on file (and will be specified in the grant agreement). Last, an internal register will be established to keep track of necessary approvals of ethics committees and competent authorities and their status (applied, obtained, conditional, to be renewed etc.). A consortium member (currently [redacted]) will be responsible for establishing and up-dating this register. The register will be checked by the DMEB (Data Monitoring and Ethics Board) on a regular basis (e.g. every 6 months).

Human issues. Embryos/Fetuses

Our research does not use primary human fetal tissues/*cells* – but we do carry out *in vivo* MRI imaging studies of fetal brain and placental development. We already have ethics approval for this *in vivo* work (attached –please see appendix).

Human issues. The need for MRI and genetic and biomarker studies in fetuses, infants, and children.

We do not directly use embryonic or fetal tissues. However, as noted above, we will carry out prospective *in vivo* longitudinal studies of fetuses and infants at low and high familial risk for ASD, and recruit a new cohort of preschoolers with ASD, typical development or other conditions. This approach is critical to identifying stratification biomarkers that precede the onset of clinical symptoms; understanding the cascading effects of genetic and environmental risk factors on brain development that ultimately lead to autism and related conditions; and identifying proxy biomarkers for treatment outcome that could be used to determine whether early treatments are working before behavioral symptoms fully consolidate. It is essential that we start this work in fetal development because we know that the causative mechanisms of ASD begin from conception. However, that the longitudinal nature of our studies recognizes that informative results will likely come from the integration of data across timepoints, rather than relying upon solely any single timepoint.

The pathophysiology and aetiology of ASD are poorly understood. Given that brain abnormalities are likely to precede the expression of symptoms, and the early onset of ASD in the first years of life and the typical manifestations of ASD at childhood age, a detailed investigation of the neural, cognitive and biomarkers underpinnings of these disorders only carried out in adolescent or adult patients will not be able to fully address our research questions. Studies in adult patients are unable to address the very important issue of the development of cognitive functions and neural systems (e.g. the trajectories of the brain circuits, and the connectivity between different areas of the brain) and lack relevance for our understanding of the origins of these disorders. Thus, it is necessary to work with fetuses, infants, very young and school age children.

Our procedures have been risk assessed and ethics approval has already been obtained for all *in vivo* fetal and infant work. It is particularly important to note that all the fetuses we study are older than the legal limits for termination in all EU countries. This means that it is very unlikely that any fetal biomarker we discover in the third trimester could have future utility in guiding decisions about termination. However, it could help parents select appropriate treatment strategies that they could use in very early development, including parent-mediated strategies that have efficacy and were developed by our partner teams (BC).

Human issues. Care and protection of research participants and vulnerable individuals

All study teams are linked to hospitals with 24h urgency services per day, and the imaging centre for fetus and newborn studies is based within a neonatal intensive care unit with full intensive care facilities, and close to a large, well-staffed maternity unit. All study procedures will be designed to minimize burden of the patients. Study staff will have relevant experience – e.g. working with pregnant mothers and fetuses (e.g. neonatology), infants, child and adolescent psychiatry and neurology and paediatrics. Invasive examinations will be reduced to a minimum to minimize burden (e.g. frequency of blood-drawing). Local anaesthetics can be provided if requested in the case of drawing blood and instruments/tools will be used which are appropriate to the age of the patients (e.g. 22 G needle for collecting blood samples). No examination will be conducted against the will of the patient or the caregiver. Dosages of any medications used in adults during pharmaco fMRI experiments in WPs 2 and 3 will be selected on the basis of relevant previous studies and are in the range that has been shown effective and safe in previous studies. Safety assessments will guarantee detection of adverse effects and a high standard of patient's safety, which will be higher than in routine care at present. Patients in the placebo group of pharmaco fMRI experiments, or clinical trials, will not be devoid of a standard and effective treatment. Certain special populations will be excluded from participation in the trial. Pregnant and breast feeding women will not participate in pharmaco fMRI experiments or clinical trials. Concomitant medication which increases the risk for adverse effects by possible drug interactions will not permitted and therefore safety of participants will increase.

Human issues. Balancing benefits against risk and burden

Benefits.

Best standards of safety assessments which are rarely used in standard medical care will be provided for participants in the human studies. Last, a biomarker for later adverse outcomes could create potential ethical problems if the condition is untreatable, and we have considered this problem. First, this is not an uncommon problem in paediatric medicine, where the routine practice of universal early examination of infants to discover potential problems is of great value, but where the possibility of detecting untreatable conditions is always present. Second, early detection allows parents to be aware and symptomatic care plans to be developed. Third it allows infants to gain the advantage of inclusion in clinical trials of potential treatments at an early stage where success is more likely [122, 123]. Last, ASD is not an untreatable condition – and it can respond to early intervention [124-127].

Minimising risk and burden.

MRI. MRI scanning is carried out by professional teams with longstanding experience in using it with fetuses/infants/children/adults for both clinical and research purposes. Together we have many decades experience with research using human MRI and we include the premier centers for neurodevelopmental research using neuroimaging in Europe. The technique is non-invasive, and does not require administration of any contrast agent or ionizing radiation. It is generally accepted that non-invasive imaging by MRI carries minimal risk in general, no long-term harmful effects of MRI are known, and if requested we can provide data that shows this remains true in the specific population(s) under investigation [122, 123]. Provided appropriate precautions are taken regarding metallic objects, there are no known adverse effects. All research subjects (e.g. infants/children and parents) will be screened for metallic objects in clothes or inside their bodies and infants will be undressed to check for the presence of metallic clips etc.

The MRI-procedure is painless and not uncomfortable, and considerable work has been done by the imaging team to define comfortable and safe positioning for mothers, and secure swaddling for infants. However it does require subjects to lie still with the head and part of the body in a tunnel-like device. Also, the MRI scanning procedure requires confinement in a small partially enclosed space. Some individuals find this to be uncomfortable and may exhibit symptoms of claustrophobia including nervousness, sweating or other minor discomfort. The sound of the MRI scanner can be quite loud. These side effects are minimized by appropriate screening and preventive procedures: children and adults (including mothers) are protected with noise-cancelling headphones, and infants with dental putty earplugs, proprietary ear defenders, and an acoustic shield. In our experience infants (when sleeping) and children/adults do not find the experience particularly problematic. Throughout the session subjects will be continuously monitored using visual and auditory channels as well as a pulse oximeter to ensure that they are comfortable, and contented. Should any infant/child/adult show any sign of distress the session will immediately be terminated. The parent or guardian will also be informed that they can terminate the session if they have any concerns. Where relevant a doctor with paediatric experience will be present during the scans. We aim to scan infants and young children in natural sleep, however in children older than 3 years some parents use sleep aids such as melatonin or Benadryl if their child is 'grizzly' and unable to settle. Where this is the case then we will follow this usual practice if requested by parents. This is has been agreed through our risk assessment and ethics procedures

We will also invite parents and their young children involved in MRI studies to attend for a "mock scan" visit if they wish. The mock scanner is a non-functioning MRI scanner which is used to practice scanning procedures and acclimatise research participants to the scanner. Although this involves the potential inconvenience of an additional visit, we would reimburse time and travel costs and we believe that the inconvenience is far outweighed by the additional benefit of allowing the parents to give fully informed consent by seeing first-hand exactly what is involved, and that this will increase the likelihood of a successful scanning session. We will reimburse reasonable travel costs and provide compensation in line with the approved protocols for research at each site. In our experience so far, parents are primarily motivated by the desire to engage in research and would consider this adequate compensation for the time and inconvenience involved.

We also argue that while the benefit for some participants will be limited, all scans are reported by a radiologist and there are some groups where the data may be of medical benefit: for instance children with ASD may benefit from early MR imaging in the short term if a primary condition is diagnosed (e.g. a tumour causing epilepsy), and retrospectively if biomarkers for subsets and treatment groups is defined by the project that can guide later treatment. Potential anxiety is addressed by preparing subjects for the MRI in a protocolised MR simulation (for more details see below). Before and after the simulation, the children, their parent and the researcher each rate anxiety on a Visual Analogue Scale (VAS). If a child does not successfully complete the simulation session, or indicates verbally that he or she no longer wishes to take part in the study, or if either the child, the parent or the experimenter assesses the child as too anxious, the MR scan is cancelled. We also are able to carry out our imaging during natural sleep in children if that is deemed helpful to an individual.

MRI sessions have breaks to accommodate the ability of mothers and children to be engaged in an MRI environment for a long time. Invasive examinations are minimized to lower the burden of the patient by study examinations. All study examinations are designed to the principle of minimizing the burden (e.g. collecting several blood samples for genetic tests, chemistry etc. by one puncture of the vein). Local anaesthetics are provided for minimizing pain by blood drawing.

Electrophysiology. For electrophysiogical recordings painless recording sensors are comfortably placed onto the infant's/child/adultsadults head using an adjustable cap. In babies this adjusts with Velcro and lace at the back and sides and has a ribbon underneath the chin so that the headgear can be resized for each baby. The fibres are wrapped in coban so that

they lead away from the infant and parent out of the infants reach. During the experiment, the infants sit on the parent's lap or on an infant chair (with the parent next to them) and watch a computer monitor or a stage, which presents them with various visual stimuli (abstract geometric forms, photographic or schematic faces, images of other objects, short videos of simple human actions, etc.) that may be accompanied by auditory stimuli (pure tones, environmental sounds, recorded or synthesized human speech) presented through loudspeakers. None of these stimuli are frightening or elicit distress, and all of them are presented well within the level of comfort and safety limits of human sensory organs. The infants' behaviour is monitored by an experimenter through a video camera, and recorded to a digital video tape for off-line coding. These studies usually last about 20 minutes, which is usually well-tolerated by infants in this range. The study is terminated if the infant become fussy or if the parent wishes to do so.

Eyetracking. Eye-tracking uses infrared lights to measure position of gaze. We can also use eye-tracking to learn about head motion and pupil dilation. Eye-tracking is very commonly used in research settings with infants as it is very baby-friendly. Our eye-tracking procedure is designed so that stimuli can be presented when adults/children/infants are attending to the screen. This allows us to present stimuli when (for example, infants) tell us they are ready to watch. While we record eye movements and other measures, we will study how babies respond to visual and auditory information in their environment. For example, we will show infants child-friendly pictures and videos containing social and/or non-social features (e.g. women telling nursery rhymes, toys moving, patterns). Eye-tracking will last around 20 to 45 minutes in total; we have found that this duration is well tolerated by infants in this age range.

Autonomic control. We are interested in how differences in autonomic control relate to early social, communication and attention problems. We will measure indices of autonomic control (heart rate and movement in foetuses; heart rate, breathing and perspiration in infants) using technologies that have been extensively used in fetal and infancy research. We will use these technologies at home (pregnancy) and during the participation in other methodologies (infancy e.g. during EEG, NIRS, eye-tracking, behavioural observations). This allows us to collect more information from infants without increasing testing time.

- We can record fetal heart rate using mobile sensors which can be provided for mothers to use at home.
- We have movement sensors that can be strapped to an infant's wrist. This measures activity levels. We will put a long-sleeved t-shirt on the infant so that they don't feel distracted by the sensor. This sensor is well tolerated by infants.
- A wearable system will be used to measure heart rate and perspiration. This involves the placement of four sensors on the child's back, stomach and/or foot. These sensors are well tolerated and designed for sensitive skin. This system has been extensively used in infancy research.

Near InfraRed Spectroscopy. NIRS will only be carried out in infants. NIRS uses weak light sources to measure haemodynamic changes in the brain. This can provide us with a measure of the naturally occurring brain activity in response to the presented stimuli. Our NIRS system uses a maximum of 16 pairs of light sources and 16 detectors. The laser sources conform to British standard 60825-1:1994 based on the maximum power that they can deliver and their output. The maximum emitted energy at each pair of light sources is 2 mW.

The NIRS technique is increasingly commonly used in research settings with infants, as it is such a baby-friendly method. This technique also provides an opportunity for scientific advancement, given the greater spatial resolution and accommodation of participant movement that it allows.

The NIRS headgear consists of optodes, each imbedded in a silicon and foam pad and sewn together within a soft headband (please see the photos below). This adjusts with Velcro at the back and has a ribbon underneath the chin so that the headgear can be resized for each baby. This headgear is known to be particularly good to use with young infants because it is comfortable and very quick to put in place.

We will use NIRS to help us study how infants respond to visual, auditory and/or tactile information in the environment. To study responses to visual information, we will show infants child-friendly videos containing social and/or non-social features (e.g. women telling nursery rhymes, toys moving). To study responses to auditory information, we will play social and/or non-social child-friendly sounds (e.g. laughing, toy rattling). All stimuli are designed to be safe and to be experienced as fun for infants in our age range. NIRS tasks will last around 20 minutes in total; we have found that this duration is well tolerated by infants in this age range.

Parent Questionnaires and Interviews. A number of parent-report measures will be used to assess behaviours in their child. For example in at risk infants we will ask about symptom levels in the older sibling, and family. The questionnaires and interviews provide complementary information. Questionnaires are posted to the parent before the visit or completed online. Alternatively, the researcher may schedule a time to call the parent at home and complete some of the questionnaires. The questionnaire packets are designed such that they should take 2 to 3 hours total time (across home and lab completion) per time point. Interviews will be done during lab visits or on a phone call and take 10 to 20 minutes in total for infant time-points and around 2 hours for toddler/child time-points. This length of questionnaire packet and interviews has been used successfully in our previous waves of data collection, and parents report in our feedback reports that they are satisfied with the general duration of time required.

Observational Assessments. We will also ask infants to participate in a number of behavioural observation tasks. Total behavioral testing time is around 1 to 2 hours at each time-point (depending on age and interest level). Games are all designed to be fun for infants. Parents report that their infants find our activities fun and engaging, and enjoy the testing sessions.

Blood sampling. Samples will not be taken from infants or very young children (age < 6 years); instead permission to obtain DNA from saliva/cheek swab will be requested. Local anaesthetic will be used to ensure comfort for children older than 6 years old. We will however, where possible, obtain samples of blood from the umbilical cord after a baby is born – this is painless.

Human issues. Feedback to participants of incidental findings

MRI. As noted above, all MRI scans are reviewed by a radiologist. If MRI, or other physical health abnormalities are found, a specialist (e.g. neuro-radiologist or neurologist) will be consulted. If findings are relevant to the subject's health, the family is contacted and advised to seek further medical assistance. This is indicated in the Informed Consent. A letter summarizing findings and recommendations is provided to the family doctor/care team for further appropriate action.

EEG. The data collected during our EEG study is not a comprehensive clinical EEG, however when an incidental anomaly is detected the following procedures are followed:

- Contact the responsible doctor to look at the images. In this stage the participant is not informed about the finding
- The doctor may contact a neurologist to examine the EEG.to determine the medical relevance of the finding.
- Where the finding represents a normal variant/has no clinical significance, the participant will not be informed.
- In all other cases the participant will be informed by the doctor in person and provided advice.
- A letter with findings and recommendations is provided to the family doctor/care team for further appropriate action.

Genetics. For genomic analyses, the strategy for dealing with incidental genetic findings is as follows. Genome sequencing harbours a small risk of incidental findings, i.e. potentially clinically relevant findings that are not related to the research question. To guard against such incidental findings, we will use a bioinformatic filter that will prevent analysis of genomic locations that are known to harbour highly penetrant mutations. The bioinformatic filter to be used in the study is derived from a recent paper by the American College of Medical Genetics (Green et al. 2013) containing recommendations on incidental findings. This filter includes the most frequent, highly penetrant genetic variants, which fall into the category of actionable findings. In the future, new actionable genetic variants might still be discovered, although these findings will become more rare and of lower frequency quickly, given the fast progress in gene finding for penetrant diseases throughout the last few years. In the unlikely instance of identifying an incidental finding despite the use of this bioinformatic filter at the RUMC, the research team will report the finding to a commission at the Human Genetics department of RUMC that will determine the clinical relevance. The commission will also determine whether or not the finding is actionable (i.e., the patient can be treated or the disease can be prevented). In case of an actionable finding, the research team will inform the patient's parents and they will be asked to seek genetic counselling.

Behavioural Observations, managing parental concerns and feedback to families. Families who have a child with ASD made aware of the increased risk to a younger sibling through their clinical services or public information channels. Despite awareness of the risk, parents may or may not have any immediate concerns about the younger sibling. For the younger ages, this is consistent with the emerging research findings in this area which indicate that early signs are likely to be subtle and not easily detected by parents or other observers. Services for this age group are limited and extremely variable in different parts of the EU. There are currently no validated diagnostic instruments nor interventions that can be used prior to 24 months of age. Moreover, current research on the topic is still limited and more research is required before it can be effectively translated into clinical application. In this study, every effort will be made to avoid inducing concerns in parents who were previously unconcerned about their child in accordance with the principle of avoiding inflicted insight. However, it is possible that some families enrolled in our projects will express concerns regarding their infant at some point during the study, for reasons unrelated to the study. The information sheet will emphasize that no individual feedback will be given to parents. If parents ask about signs of ASD in their child, we explain that providing feedback on specific cases lacks scientific grounds since there are currently no validated diagnostic instruments for the age of the child; in fact, developing such instruments is one of the long term goals of the study. In cases where the family does raise concerns, the research team will then respond in such a way to facilitate parents' concerns being addressed by the appropriate services or individuals. This would include encouraging them to speak to their GP, health visitor or paediatrician and offering to write a letter of support if this was felt to be helpful (which could be sent via the parents or directly, according to parental preference). Parental concerns are best addressed, monitored, and dealt in partnership between the parents and their clinically responsible health care providers, and not in the research setting.

Looking to the future – and reducing stigmatisation

We anticipate our work will lead to groundbreaking new knowledge about stratification biomarkers and treatment options for ASD. Thus, we need to not only consider the ethics of the direct experiments we are running, but also the potential implications of our discoveries. We have developed a set of strategies that we will employ as new results emerge from our project. Our over-arching strategy is to:

- *Take a proactive approach.* Work described within WP5 will involve engaging with the patient and client community to ensure that community voices are heard through every stage of the research process. We will begin discussing the

broader societal implications of the planned outcomes of our project from the outset, particularly for potentially sensitive areas like fetal biomarkers, genetic stratification or pre-emptive treatment for ASD. Our investigator teams have long histories of using similar processes to shape the research streams that feed into AIMS-2-TRIALS, and will continue to engage with the community at the site level. This will ensure that when new results emerge, we have already identified and begun to address the relevant community concerns.

- *Ensure dissemination is ethically-informed*. Sensitive public dissemination of the results of our work in AIMS-2-TRIALS will be critical. We will ensure the ethics of our dissemination in sensitive areas are fully considered by seeking the advice of our Internal Ethics Board on press releases and paper wording, who will consult our Ethics Advisor or engage other international experts where necessary. We will also continue to host webinars and public meetings around important topics and new findings as they arise, as we have successfully in EU-AIMS. This will ensure that we use the most appropriate framing of our research when we communicate it to the community and broader public. We will ensure that we publish results from our studies – and even if they are negative. Also the results from our RCTs will available through public repositories (e.g. clinicaltrials.gov and the EU clinical trials register).
- *Contribute to shaping new ethical frameworks*. Novel discoveries may require new ethical frameworks to be developed. This may be particularly applicable in the area of genetics, where the rapidity of progress will change our ability to make nuanced individual predictions. Another sensitive issue is the identification of fetal biomarkers; despite the acquisition of this data well beyond the legal limits for termination of pregnancy we recognize that there may be concern in the community. As the scientific progress within AIMS-2-TRIALS crystallises, we will contribute to shaping the new ethical frameworks required to govern use of our findings by working with relevant agencies to stimulate the development of relevant guidelines (e.g. World Medical Association; ICH; the EU commission). This will ensure that as AIMS-2-TRIALS produces the opportunity for new treatment approaches, the ethical frameworks necessary to govern their use are in place.
- *Reducing stigma.* Stigma in relation to people with neurodevelopmental disorders and/or mental illness can be understood as a combination of problems of knowledge (ignorance), attitudes (prejudice) and behaviour (discrimination). To reduce this a series of interventions have been identified which may be effective in reducing stigmatisation and discrimination at the following levels: individuals with neurodevelopmental disorders/mental illness and their family members; the workplace; and local, national and international. The strongest evidence for effective interventions at present is for (i) direct social contact with people with neurodevelopmental disorders/mental illness at the individual level, and (ii) social marketing at the population level. Hence our dissemination program will directly address each of these issues – for example our social marketing efforts include not only large scale use of social media but a progam of activities in art and science museums across the EU.

Specific WP issues

WP2. Task 2. Studying fetuses, neonates, and infants at high risk of autism; and young children with ASD.
This application involves the collection of data from pregnant women, newborn infants and young children, and samples containing DNA from infants. As noted above we already have ethical approval for all our studies in fetuses and infants (please see **Appendix W**). Nevertheless there are a series of ethical issues we will encounter including:

Recruitment, and safety of MRI, for fetuses. Mothers of 'at risk' and control fetuses will only be recruited in the UK. They are recruited by advertisement within antenatal services. Regulatory guidelines state that it is safe to use fetal MRI at 3T or less during the second and third trimester [130]. Moreover, in a recent study involving over 1.4 million pregnancies, exposure to MRI during the first trimester of pregnancy was not significantly associated with any adverse effects on the fetus or the developing child [131] . The fetal brain is most sensitive to heat during the embryonic and mid-gestation periods, i.e. prior to our scanning window [132]. In our Standard Operating Procedures, the fetal temperature is assumed to be 0.5°C greater than maternal temperature [133]. Hence, it is important to ensure that the maternal temperature does not rise by more than 0.5°C while in the MRI scanner, and that the fetal temperature is kept under 38°C. The temperature in the scanning room is therefore set to 18°C, with air-conditioning inside the bore of the magnet. The expectant mother's temperature is monitored before and after the scan. Sequences are run in an order that minimises long periods of the higher SAR sequences. The noise levels in the scanner are also kept to a minimum, and our mothers wear earplugs and headphones. There is at least a 30 dB sound attenuation as noise passes through the maternal abdomen and amniotic fluid to the fetus, and there is no evidence of hearing impairments in children who have undergone MRI examination during fetal life[134]. All our optimised sequences are acoustically tested to ensure we keep maximum noise levels at 100dB or below. Loud sequences are run for the shortest possible acquisition times.

Recruitment, and safety of MRI, for neonates. Mothers of 'at risk' and control neonates will only be recruited in the UK. They are recruited from the fetal cohort outlined above. MRI at 3T is safe for neonates [135]. Standard Operating Procedures are followed

to ensure highest safety – including monitoring of temperature, acoustic noise, and metallic implants – is in place. The infants are scanned at dedicated paediatric clinical imaging units. For example, a thorough metal check be complete to ensure that the individual is free of any ferrous metal. Exposure to acoustic noise is minimised by insulating the scanner bore with sound attenuating foam. The infant's ears are also protected with mouldable silicone-based dental putty and MiniMuff noise attenuators. In addition, an experienced clinician supervises the MR examination to monitor the infant's physiological parameters, including heart rate, oxygen saturation, and body temperature.

Sedation. We will not use sedation during any of our imaging paradigms for fetuses or infants. However in children older than 3 years some parents use sleep aids such as melatonin or Benadryl if their child is 'grizzly' and unable to settle. Where this is the case then we will follow this usual practice if requested by parents.

Informed Consent. We have undertaken MR imaging studies of fetuses, infants and children for two decades, and previously undertaken all of the procedures or practices required by this project. Each has been reviewed, most on multiple occasions by Regional Research Ethics Committees or latterly the National Research Ethics Service. In each case informed consent by the pregnant woman or parents of the infant was an essential part of the project, and in every case the review committee gave favourable opinions of the research proposal and allowed it to proceed. We are fully aware of the problems of gaining informed consent, and our processes have been independently reviewed and found to be better than those normally used in neonatal medicine [136]. For example we have prepared You Tube videos of our what families can expect during fetal [137] and neonatal scanning [138].

Fetuses and infants at−risk for autism, and children, cannot consent for themselves. Hence, informed consent will be obtained from the parent or guardian of the fetus/infant/child taking part in the study using an Information Sheet, which provides details on purpose, design and participation. The information sheet also includes descriptions of the assessment procedure where the infant's comfort and enjoyment are ensured and assessments are stopped at the parent's request or by the researchers in the unlikely case that the infant expresses discomfort.

Research in children which is not primarily for the benefit of the subject. Data collected in this study are not primarily of diagnostic intent. However, a small proportion of routine MR brain images of asymptomatic individuals show abnormalities. In some cases it will be of benefit to the individual to know about these findings (please see relevant section(s) above for more details).

Data management of parental/infant information. Data collected from parents include personal, full medical and family history, lifestyle, medication, genetic information as well as neurodevelopmental data of their children. This information will be stored and made available to the scientific community for a long period of time. As follow-up research is intended, there is a need to link data to identifiable individuals. Also through combination of data sets, individual participants may be identifiable. To address these issues fetal and infant data will be managed according to the regulations and guidance provided in each country. For example in the UK by the Health Research Authority, and in full compliance with the UK Data Protection Act 1988 which regulates the storage and use of personal data in the UK, and is in line with theEuropean General Data Protection Regulation , covering the potential issues noted above. The permission for research granted by NRES will require conformity with these legal instruments.

In particular this permission and the consent process for the study will explicitly take note that: personal data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes; personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed; that personal data shall be accurate and, where necessary, kept up to date; and that personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes.

To this end we will explicitly obtain permissions for data storage and uses in a manner consistent with the act, including the provision of specific anonymous data linked to image data to the scientific community for defined scientific projects, and all data users will be required to commit to follow the tenets and spirit of the regulation, providing appropriate data control and safety, and committing to not transmitting data for third party usage.

Data will be fully anonymous at the point of use, and linkage of data will only be possible by the dHCP team; linkage keys will not be provided to other users, only the specific datasets requested for each project.

The permission granted by NRES to allow recruitment to begin will also cover two complex data issues; facial recognition by 3D reconstruction of cranial MR images; and personal identification by whole genome analysis. Safeguards, such as facial blurring or extraction, are possible and will be used as directed by NRES.

WP2. Longitudinal follow up of LEAP cohort (children > age 6, adolescents, and adults above the legal age for consent)

Ethical permission for this part of our proposal is already in place across all our centres; and approval letters have already been lodged with the IMI. The issues around use of sedation and determining capacity/obtaining informed consent have been discussed above. Blood samples be requested from young children at age >9: and permission to obtain DNA will be requested. We will also seek permission to take blood samples from adolescents and adults. If that is refused then permission to obtain DNA from saliva will be requested. We prefer to use blood for DNA where possible as it provides a better yield.

The issues pertaining to imaging and electrophysiological measures have been discussed above.

We anticipate that some families/individuals may not wish to return in future years. This issue has also been discussed above

WP2. Neurochemical Imaging (PET/autoradiography) methods for understanding epilepsy [WP2]

The objective of this part of WP2 is the use of PET imaging to examine endogenous transmitters and/or synaptic development in adult patients and healthy volunteers. **Infants and children beneath the age of consent will not be included in PET studies**. The PET centre at KCL has conducted approximately 5000 scans per year since opening in 1991 and over 30 drug development-related studies in the last 3 years using novel radiolabelled probes. The PET centres at the KI and UC are equally experienced. In general the experimental conditions have been tolerated well by the subjects. There are two major concerns with PET imaging – the direct response to the injected radioligand and the possible effects of radiation exposure. The injection of a tracer dose (typically less than 10 micrograms total per subject) of a radioligand has not had any pharmacological effects in nearly 10,000 studies worldwide and it is widely regarded as safe and tolerable – so long as it is done per the standard and well established procedures. Some subjects may experience transient pain and discomfort from blood vessel cannulation – this is clearly specified in the informed consent documents. The studies will meet all current EU requirements as described in the "Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU" [139] and approved by the Radiation Safety Committee of the Karolinska University Hospital. Accordingly, the radiation dose is limited to below 10 mSieverts.

The work will be approved by the Ethics Committees of Stockholm and Coimbra and the national Integrated Research Application System [IRAS] system in the UK, and conducted in full compliance with the Declaration of Helsinki (and Declaration of Madrid when psychiatric patients are included). Subjects will be included after written informed consent. They are covered by the general insurance of the Swedish, Portugese, and UK health care systems and free to withdraw their consent without any explanation or further consequences.

Incidental findings such as unexpected brain anomalies will be followed up by appropriate clinical functions at Karolinska University Hospital for Swedish volunteers, University of Coimbra for Portugese participants, or Kings College Hospital for those in the UK. The studies are prospective and will not include collection of previously collected data. All image files and subsequently generated data in the quantitative analyses will be assigned a code. The key will be stored in a locked safe accessible to one person only. The studies will be conducted in compliance with the relevant Swedish, Portugese, and UK Biobank Laws to ensure adequate protection of data and privacy.

We will also validate our findings using autoradiography on brain tissue resected as part of normal operative procedures for treating epilepsy at KCL. To be clear - we will not remove any additional tissue for this study, we will only use tissue that is normally resected for clinical purposes. This will require specific consent from the individual. Also autoradiography will be performed on resected epileptic tissue after clinical neuropathological examination. Subject to ethical approval and informed consent, tissue will be stored and analysed in compliance with the UK Human Tissue Act (2004). Paper copies of consent will need to be held for **7** years, and electronic for **30** years. Some tissue may also be exported and shred with other non UK collaborators (e.g. UCB). Patients will need to give specific consent for this to happen. Also we will follow Code of Practice 8 of the UK Human Tissue Authority which states 'Exported material should be procured, used, handled, stored, transported and disposed, in accordance with the consent which has been given, with due regard for safety considerations and with the dignity and respect accorded to human bodies, body parts and tissue in codes in England, Wales and Northern Ireland. This includes providing donors with adequate information upon taking consent, that their samples may be transported as exported samples for use abroad. [140]

WP2. Functional imaging/EEG models for drug testing/discovery.

One objective of human experimentation in these WPs is to establish cross-species homology and to identify specific brain activations which may serve as targets for drug development. The main focus of this work includes MR Imaging and EEG, though personal and genetic data will also be collected.

The issues pertaining to imaging and electrophysiological measures have been discussed above. Personal (epidemiologic) and genetic data are being collected as part of this study. Since linking genetic information to multimodal imaging and outcomes data is at the core of our work, the collection of this data is necessary. Specific consent for this is obtained. Data are pseudo-anonymized. The amount of sample donation will not exceed national and local regulations, neither the amount specified in the informed consent leaflets.

WP2. Metabalomic and other biomarkers for autism.

This work package requires the analysis of blood samples (serum and plasma) from both existing studies and our new studies. This will include samples from patients with psychiatric symptoms - and in WP 3 and 4 those before, during and after drug treatment with a view to identifying and validating biomarkers with potential utility to aid the diagnosis and treatment of diseases such as autism. Written informed consent has been obtained in all the current available samples being considered; and will be obtained from new patients by both academic partners and **EFPIA** member companies carrying out any future clinical trials in

accordance with EU ethical standards and local institution/country review board requirements. For data from other studies that may seek to collaborate with us in future the academic and **EFPIA** applicants will review the informed consent to make sure that the subjects have consented to have their sample used for the scope of the present research. No patient's samples will be included in the biomarker study without informed consent. For anyone in our LEAP study who reaches their age of majority (>16) and who asks for their data to be removed, this will be complied with.

Only fully trained clinical staff will take and process blood samples. Standard blood doning and sample handling protocols will be applied in all centres. Samples will aliquoted and stored at -80°C, and will be blinded and anonymized by providing a specific code for each patient before shipment to the Leboyer labs, for biomarker profiling. This code is subject to data protection in accordance with EU laws. No data enabling the identification of patients or volunteers will be provided to sample users. As no intervention will be decided on the basis of these studies, and as it is highly unlikely any biomarker data would be available in a timescale useful for the acute treatment of the patients, there are no plans to provide any follow up information to the patients.

Since a key feature of this application is to translate clinically relevant features of psychiatric disease into better and more useful preclinical models to enable more efficient and targeted drug discovery – the WP will also include the testing of biomarkers in samples from animal models that are generated in the course of WP 2 and/or are already available with **EFPIA partners**. The animals will be housed, cared and treated as laid out in the sections dealing with other WPs above – only their terminal samples will be sent to this part of the WP for analysis. This element of validating animal models by examining them for biomarkers will in time lead to the further refinement of models and could also lead to the reduction of the total numbers of animals used in development.

WP3. 'Shiftability' and Fast Fail Trials.

The issues of consent, compensation for time, and procedures to be used (e.g. MRI and EEG) have already been addressed in prior sections.

A particular risk of these components are those of safety and tolerability of the pharmacological compounds we may use.

Part of WP3 will entail the administration, to adults only, of a pharmacologic challenge – (e.g. one dose of an SSRE) to assess the effect of these compounds on brain function. All of the compounds which we investigate will be safe for the intended purpose, and approved for use in adults. In addition, these interventions will be restricted to Partners of our network which are fully equipped for clinical research and where a research nurse and a doctor will monitor the patients. Patients will be informed verbally as well as in writing (via the patient information sheet) about the potential side-effects of any pharmacological probes. In the interest of patients' safety, any patient suffering from moderate to severe hypertension, hypo/hyperthyroidism, history of drug or alcohol abuse and epileptic seizures will not be included in pharmaco-challenge studies. Pregnant and breast-feeding women will not be included because of potential embryotoxicity. Thus, a combination of an experimental design informed by previous experiments, careful patient selection, appropriate consent procedures, dedicated facilities and monitoring will allow us to conduct this study in a manner that minimizes risk.

The doses of medication we have initially chosen were selected to minimize possible side-effects with maximium likelihood of target engagement. We have previously adopted this approach for single dose studies of a range of compounds and found excellent tolerability in all our studies so far. With regard to the specific compounds.

A) Tianeptine. The medication tested in this study (tianeptine) is manufactured by pharmaceutical company Servier. We will use the manufacture's recommended dosage of tianeptine - 12.5 mg/tid. We already have ethics approval in place for the 'shiftability' study at KCL for cases vs controls, and we will now seek an amendment of this to allow intra-ASD comparisons. We will need to also obtain ethics approval at UC; and for the 'fast fail' study in both centres. Tianeptine is generally well tolerated and has been described as having a safety profiles [141] similar to other antidepressants and anxiolytics. The side effects profile is much like SSRIs, and includes nausea, constipation, abdominal pain, headache and dizziness. Clinical trials in healthy controls of 12.5 mg/tid have reported no adverse effects on cognitive, cardiovascular or psychomotor performance. When compared to placebo, only headache appeared more often with tianeptine. In a placebo-control trial in [142] patients with major depression the most commonly reported side effect(s) included nausea (8%), constipation (14%), headache (16%), and dry mouth (8%). A comparison of tianeptine to the SSRI paroxetine, in patients with depression and anxiety, reported the following side effects for tianeptine: nausea (7%), headache (6%), insomnia (1%) and dizziness (1%). Overall tolerability for tianeptine was significantly better than paroxetine. There has been one published report of a suicide death due to an overdose of Tianeptine in combination with alcohol [143]. At the single doses we plan to use, we do not expect to see significant adverse effects. Nevertheless, a clinician will review each participant before and after drug administration. Also, the participants will be asked to stay at the research unit until at least 4 hours after drug administration. Before leaving, each participant will complete an 'adverse effect checklist' with the clinician who will act on any concerns as appropriate. The randomization code can be broken at any time during the session. In the 'fast fail trial' all participants will be prescribed a 4 weeks' worth of tianeptine at a time by a registered doctor, which they will receive from the pharmacy at the outpatient department of the Maudsley Hospital and/or UC. Standard clinical guidelines will be followed. We will write a letter to the participants General Practitioner (GP) informing them of their patient's choice to take part in the study. We will include a product summary of the medication the patient is taking. Safety will be monitored by a medical doctor.

B) AZD7325. The company have furnished the PI with the Investigator Brochure for AZD7325 (This will be shared with the IMI if requested). The compound has been used in five Phase I and two Phase II studies in the US and EU. Single dose acute studies have used up to 100mg and fixed dosing of up to 15mg BID have been investigated. Across these studies AZD7325 has been well tolerated. Adverse effects are dose dependent and not prominent at the doses selected for this study. The most common adverse effects reported include dizziness, somnolence, fatigue and headache. Also reported, but less common, were; feeling hot, euphoria, feeling "drunk", and nausea. At the single doses we plan to use, we do not expect to see significant adverse effects. Nevertheless, a clinician will review each participant before and after drug administration. The participants will be asked to stay at the research unit until at least 4 hours after drug administration. Before leaving, each participant will complete an 'adverse effect checklist' with the clinician who will act on any concerns as appropriate. The randomization code can be broken at any time during the session.

WP4. Clinical trials.

WP4 will conduct 2 RCTs. RCT1 will be a randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of arbaclofen in children and adolescents (ages 5-18) with autism spectrum disorders. RCT2 to be conducted in part 2 will be determined based on results from other WPs and availability of a novel compound by industry or academic partner. These studies will be conducted according to the principles of the World Medical Association Declaration of Helsinki and its most recent amendment (Fortaleza, Brasil, October 2013). The Investigator will conduct all aspects of this study in accordance with all national, state and local laws of the pertinent regulatory authorities. Privacy laws and regulations will be adhered to during all procedures related to studies in WP4. The clinical trials will be conducted in accordance to the Regulation EU No 536/2014 (https://ec.europa.eu/health/human-use/clinical-trials/regulation_en). This Clinical Trial will also follow the guidance in 'Good Clinical Practice: Consolidated Guideline' (ICH E6) adopted by the ICH, 1 May 1996 and the protocol developed has followed the Statistical principles for clinical trials [144].

The issues of consent, compensation for time, procedures to be used (e.g. blood draw and EEG) and ethical aspects regarding sample use have already been addressed in prior sections.

Regarding the compound to be used in RCT1, arbaclofen, there has no been significant safety or tolerability concerns from previous studies with the drug in children and adolescents. The dose used have been previously used for the age range to be included in the study. The most common adverse events reported have been agitation (22%), irritability (22%), fatigue (16%), psychomotor hyperactivity (16%), diarrhorea (13%) and insomnia (13%). The majority of AEs were mild and resolved spontaneously or with dose adjustment. More recent studies published in a) animal models given R-Baclofen show that the compound had produced minimal side effects and b) human studies with children and adolescents arbaclofen was well tolerated with affect lability (11%) and sedation (9%) being the most common adverse events. Racemic baclofen and arbaclofen are excreted renally. Any participants with renal disease will be excluded from the study. Pregnant or breast feeding women will also be excluded. In addition, females of childbearing potential who are sexually active will have to agree to use an accepted form of contraception.

Pharmacokinetics with arbaclofen has been assessed in paeadiatric population (2-17 years, n=61) with cerebral palsy [145]. Forty-nine subjects had at least one post-dose PK blood sample and were included in the population pharmacokinetics (PopPK) analysis. R- and S-baclofen showed identical concentration-time profiles. Both baclofen enantiomers exhibited linear and dose/kg-proportional PK, and no sex differences were observed. Average baclofen terminal half-life was 4.5 hours. A 2-compartment PK model with linear elimination and transit absorption steps adequately described concentration-time profiles of both baclofen enantiomers.

Safety will be assessed by evaluating reported AEs, suicidality assessment, clinical laboratory test results, ECG findings, physical examination findings and concomitant medication usage.

To assure the continuance of strict pharmacovigilance, an independent Data Safety Monitoring Board (DSMB) will be constituted to review the safety data collected in the study (including AEs, physical exams, vital signs, clinical laboratory tests, suicidality assessments, ECGs, and/or other information necessary to determine subject safety). For more information on the role and procedures of the DSMB see the RCT1 study protocol.

The Principal Investigator at each site will have extensive clinical experience caring for patients with ASD. The Principal Investigator or a designated substitute will be available 24 hours a day, 7 days a week. We will set up a 24/7 emergency unblinding system with each centre pharmacy. Results of the physical examination and laboratory values will be evaluated by the staff at each center for evidence of immediate safety concerns or for changes that indicate safety concerns. At each clinic visit and phone call during the study period, investigators will question parent/caregiver/legal representative about changes in health, inter-current

illnesses and concomitant medications. Any AE (adverse event) will be documented regarding the time it occurred, duration, severity, and relationship to the study drug. The Investigator will have to report promptly all SAEs to the sponsor in accordance with the procedures detailed in the RCT1 protocol. The Investigator, or responsible person according to local requirements, will comply with requirements related to the reporting of SAEs (serious adverse events) to their IRB or Independent Ethics Committee (IEC). For more information on reporting adverse events see the RCT1 study protocol.

WP6. Analysis Methods

This part of the WP mainly entails the analysis of cognitive, behavioural, electrophysiological, genetic, and scan data already collected in prior projects by our partners and as part of these WPs, though some specific and targeted MR image acquisition will be required over the five years. The acquisition and use of this data is governed by specific ethics applications for each clinical project. A broad ethics application has previously been granted to all our clinical recruitment sites involved in WP2 who will feed data to WP6. That allows data to be stored pseudoanonymously and securely on computer systems within all our clinical recruitment sites for possible future research ("Establishment of an MRI library of normal and diseased brains of adults and children", 033/03). We will use this stored data (and others for which appropriate informed consent was obtained by the academic and/or industry partners) to train, test and evaluate new software being developed by our network. To make full use of data collected in clinical research studies they must be analysed with computer software. To be able to develop, debug, test and evaluate such software requires access to larger amounts of data from a wider variety of subjects than are usually collected for individual projects. These data are needed to train and test the software and in particular to ensure that it can cope with age and sex differences and the subtle variations in (for example) the appearance of the brain caused by the range of neurological and neuropsychiatric conditions that are the basis of this IMI project. We also propose to pool data (e.g. electrophysiological recordings and brain scans) acquired and stored during previous research studies by our network and partner companies to test and evaluate future analysis techniques.

Informed consent issues. We will be analysing data from both new and existing studies. Research participants will have passed the inclusion criteria associated with those specific studies. We will include data from all subjects unless (a) they have not consented for their scans to be used in future work (b) the analysis technique under consideration is not appropriate for their clinical status or data−type (c) there are technical problems with the data (e.g. loss of quality caused by movement during a scan) (d) there is a risk of breaking anonymisation by inclusion.

Data protection issues. Some limited demographic information (age, sex, handedness, clinical status only) may be requested from the PI of the original study for certain kinds of testing. If supplied this data will be linked to the data using an existing pseudo−anonymisation code, for which only the study PI has an unblinding list. In this case researchers working under this ethics proposal will have access to these pseudo−anonymised demographics only − unblinding is not required at any stage of technical evaluation. These pseudo−anonymised demographics will be stored electronically and securely on central computers.

WP6. Identifying risk pathways via Genetics

The major objective of this WP is to collect genetic, transcriptomics and clinical data and link them to understand pathways of illness and their relevance to drug development. The major ethical issue in this effort are those related to consent, data protection and privacy of subjects.

AIMS-2-TRIALS has already genotyped ~ 1000 subjects, and will acquire genetic samples from ~ 10,000 more (including follow up studies of 1500 infants (now children) from the EU infant connectome project and the 7000 infants (now children) from the Safe Passage Study (South Africa). Phenotyping will be done by researchers (e.g. psychiatrists and psychologists) blind to genotype status. Standardized interviews and questionnaires used worldwide for diagnosing psychiatric patients will be employed.

In view of the continued expansion of data related to human genetics, concern for protection of the personal privacy of individuals who participate in such studies is paramount. While some have advocated the use of complete anonymity as a way out of this dilemma, others argue that the future cannot be predicted, and that future benefits may be lost when the link between genetics data and the individual subject is totally lost. Therefore, some ethical bodies have suggested a reversible third-party encryption system.

EFPIA members and Charity partners (e.g. SFARI) may also contribute data and data analyses from clinical trials (or other work) that were generated before the start or during this grant. The data analyses shared within this WP will be generated in line with the scope of the respective study protocols and the corresponding informed consent forms. Also, only samples from subjects enrolled in clinical trials that have been collected according to GCP standards, and include informed consent for the type of analyses performed in WP6 will be contributed to this WP. In addition, all samples will be handled according to Standard Operating Procedures (SOPs) within the contributing industry partners. These SOPs ensure that the privacy of individuals participating in clinical trials is protected, e.g. by (double) coding samples obtained from participants and restricted access to the keys holding the codes.

Based on the above, there may be a small set of samples/data where the participant has provided the consent for the use of data, but, not for the sharing of samples; and in some cases for the sharing of the results of analysis rather than the raw data itself. In such cases, biological analyses will be performed through the respective owner of the clinical trial samples (i.e. the respective **EFPIA partner**) and only the resulting and consented data or results of analysis (as allowed per initial consent) will be shared. All efforts will be undertaken by the participants of this WP to ensure that only those biological samples will be contributed for which the respective informed consent covers the planned analyses, e.g. CNV status and transcriptomics and association of these molecular markers with the treatment response. Samples for which the informed consent does not cover the scope of the analyses outlined in this WP, will not be used, unless a new and revised informed consent is obtained. In view of the multi-centre nature of most clinical efficacy trials, a re-contact of subjects from previous clinical trials would be a major logistical effort and is currently not planned by us. This possibility will only be pursed if there is an acute need for more samples – in which case the allowance in the original consent form will be strictly adhered to.

WP6. Identifying biomarkers of response and personalized medicine – a focus on the predictors of outcome and pharmacogenomics of autism. Data Protection issues.

The issues around consent, and 'deep phenotyping' (e.g. EEG, imaging, cognitive and behavioural assessments and genetic material) have already been discussed above.

In this part of the work package, however, we may also combine our data with samples previously collected in a number of studies for the research on the clinical and genetic determinants of treatment response in autism. Such re-use of combined existing data presents an opportunity to derive large benefits with no or very little additional burden on participants. However, as this project includes genetic samples and sensitive data including information on participants' mental health, the project raises issues with regard to informed consent, data protection and handling of biological genetic samples.

It is paramount that any research performed with previously collected data conforms to what the participants consented to be done with their data. The academic and EFPIA applicants will have reviewed the informed consent to make sure that the subjects have consented to have their sample used for the scope of the present research. Specifically, all participants will have consented that the data and samples they provide would be used for the research on autism treatment and its genetic determinants. Before any sample would be shared between EPFIA member and IMI collaborators, availability of informed consent for each of the research subjects would be checked. Furthermore all Academic and EPFIA partners would make sure that all samples to be investigated as part of this project have obtained appropriate approval by local Ethic Review Board committees to be used for the same research aims as the present project.

As the proposed research includes use of genetic and mental-health related information, adequate data protection procedures have to be in place to prevent inadequate use of such sensitive data. We take several precautions to comply with the highest standards of data protection. First, we limit data collection and sharing to data immediately relevant to the research questions. The data will be fully anonymised and no personally identifiable information, such as name, initials, date of birth, or address will be included. There is no need to re-contact research participants and therefore, data is not only anonymised but also unlinked so there is no possibility for the researchers to reverse the anonymisation process. The anonymised and unlinked data will be stored exclusively on password protected servers and will be only accessible to approved individuals who are researchers on this project.

Research with human participants will be conducted in the countries listed below in accordance with national and international regulations.

EU countries	
Country	*Applicable National Regulation(s)*
France	French Public Health Code, Legislative section, First part: general protection of health, First book: personal protection, Second Title: biomedical research, ch. 1 to 3 (this law also lists the relevant national authorities for regulatory and ethical approval). Ibid., Third Title: genetic examination. Ibid, Fourth Title: Tissues, cells, human body products and their derivatives. In the French Public Health Code, related regulatory parts on biomedical research. Loi n° 78-17 du 6 janvier 1978 on Data Protection and Liberties, art. 2, 53-61.
Germany	Arzneimittelgesetz (AMG) 24.08.1976, last amended 07.07.2017 (this law also lists the relevant national authorities for regulatory and ethical approval); GCP-Verordnung (GCP-V) 09.08.2004, last amended 19.10.2012, Arzneimittel- und Wirkstoffherstellungsverordnung (AMWHV) 03.11.2006, last amended 28.10.2014; Berufsordnung für Ärzte (Medical Association's professional code of conduct);
Ireland	The European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004. The Control of Clinical Trials Acts 1987 to 2006 (for any other clinical trials on medicinal products not covered by the above Regulations).

	No other legislation is involved for other clinical research projects. Good Clinical Practice (GCP) regulations and the requirements of the Research Ethics Committee of St. James's and Tallaght Hospitals.
Italy	Ministerial Decree of 15 July 1997: Transposition of guidelines of the European Union in good clinical practice for the conduction of clinical trials with medicines" Legislative Decree no.211 of June 24, 2003: Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use" Ministerial Decree of May 12, 2006: Minimum requirements for the institution, organization and functioning of Ethical Committee for clinical trials with medicines Ministerial Decree of 14 July 2009: Minimum requirements for insurance policies which safeguard participants to clinical trials of medicinal products Determine n. 451 of 2016 "Requirements for Phase I Centers" Ministerial Decree of 21 December 2007 "For the Request for Authorization to the Competent Authority and the Ethics Committees" Regulation n. 536/2014 of 16 April 2014 "New European Regulation on Clinical Trials of Medicinal Products in Europe" Ministerial Decree of 8 February 2013 "Criteria for the composition of the Ethics Committees that integrate the DM of 2006" Ministerial Decree 17 December 2004 "For non-profit studies"
Netherlands	Local Ethics approval from an accredited Medical Ethics Committee (METC) and positive judgment by the local authority according to the Medical research involving human subjects act (Wet Medisch-Wetenschappelijk Onderzoek met Mensen- WMO) (see www.ccmo.nl) Declaration of Helsinki De Nederlandse Gedragscode Wetenschapsbeoefening (Rules of Conduct for Scientific Studies of Dutch Universities) (see www.vsnu.nl) Wet Bescherming Persoonsgegevens (see www.cbpweb.nl), in accordance with the European Data Protection Reform (see www.ec.europa.eu) Good Clinical Practice Directive EMA: European Clinical Trials Directive Local: Approval by the Data Protection Representative of each partner
Spain	Biomedical Research Act 4/2007; Royal Decree on Biobanks 1716/2011 Royal Decree 1090/2015 (RD 1090/2015), of 24 December, governing the conduct of clinical trials with medicinal products.
Portugal	Directive 2005/28/EC or Good Clinical Practice Directive, of 8 April 2005 of the European Parliament and of the Council, lays down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Directive 2001/20/EC or Clinical Trials Directive of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, Regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. European General Data Protection Regulation on the protection of individuals with regard to the processing of personal data and on the free movement of such data. The EU Charter of Fundamental Rights; Helsinki Declaration (adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964; amended bythe 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy,October 1983; the 41st World Medical Assembly Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000); Universal Declaration on the human genome and human rights adopted by UNESCO; Applicable National Regulations: monitored by Entidade Reguladora da Saúde, CEIC and INFARMED. The conducting of clinical trials on medicines for human use is governed by Law n.º 46/2004 of 19 August that implements Directive 2001/20/EC of the European Parliament and of the

	Council of 4 April in Portuguese legislation. Approval by local review boards will be obtained, and all trials will be registered in the PNEC portal.
United Kingdom	The Medicines for Human Use (Clinical Trials) Regulations 2004 SI 2004/1031 (providing standardisation of procedures for ethical and competent authority consideration and authorization in the UK), last amended 2008 (SI 2008/941). The Human Tissue Authority Code of Practice 8. The UK Human Tissue Act 2004 (c30).

5.1.1 Human Cells/Tissues

All tissue samples will be held and handled in compliance with the UK Human Tissue Act 2004 (c30).

Most of our work involves the use of established cell lines of human origin. They raise few ethical issues since as established lines, anonymised in accord with current European regulations, they fall outside of the legislation relevant to primary human tissue and require no contact with patients or primary human material. We will, however, also generate new human lines, and this raises ethical issues that we will address.

The novel lines will be generated from hair biopsies taken from ASD patients and control individuals. The main issue here is informed consent, anonymisation, and procedures for the appropriate storage and access to material. This consent procedure must accommodate the fact that many of the patients are children, and others who might not be able to give informed consent. At **KCL**, we have established a protocol for this informed consent, and routinely collecting scalp hair biopsies for the generation of iPS lines. We have generated information datasheets for children and parents/carers, including an appropriate level outline of the biopsy procedure and the intended use of the sample. We have specified procedures for the collection, anonymisation, and storage of this material, and the lines derived from it. The protocol has been reviewed by our local ethics committee, and received approval. We intend to use this established protocol, appropriately amended to meet local needs, as the prototype in extending our project to other centres as required.

5.1.2 Management and Protection of Personal Data

Data Management (WP6).

Within AIMS2-TRIALS we will (through WP6, lead by RUNMC, IP, Roche) institute a data management structure based on the Pasteur Data Warehouse solution (PaDaWan). This structure will integrate all data sets collected in WPs 1-4 and meets digital security and data management standards on the basis of FAIR principles.

RUMC and IP will establish an informatics platform for safe, secure data storage and deliver end-to-end privacy protection for sensitive data while enabling full data access functionality and implementing the principles of ‘data security by design’, meeting the legal requirements of the EU General Data Protection Directive (GDP Regulation (EU) 2016/679).

The security and access rights procedures will take into account national, and international legislation so as to ensure - with our US and other partners the legal, ethical, and efficient reuse of data by the scientific community.

Participation in the consortium as data will require any partner organisation to adapt the EU-AIMS2-Trials consortium Data Management Plan and include any applicable national regulation (see appendix for the example template). Access to budget and data from the consortium will require the partner to complete the consortium DMP along with any local institutional DMPs and submit copies to IP along with written confirmation by the local institutional Data Protection Officer (DPO) that allm data data handling and storage activities follow local institutional, national as well as international laws and proceeds according the requirements of the local ethical institutional review board.

Open Access Data will become available to those who register an account with the AIMS2TRIALS consortium and agree to the Open Access Data Use Terms. This includes agreement to comply with institutional rules and regulations.

Investigators are expected to meet one of the following criteria to be qualified to receive access to AIMS2TRIALS Data:

1. You are a Principal Investigator (PI) of scientific research at a university, a research organization (including commercial entities) or a government agency who is the leader of a laboratory or research team or who is working independently; or
2. You provide the name of the PI who is overseeing your research and is approved for access under #1.

3. If you do not meet either of the above criteria you may be considered qualified based on a track record of scientific publications or on the basis of a written reference from someone who meets qualification #1, verifying that the data will be used only for the purpose of legitimate scientific research.

The Open Access Data Use Terms will require a legally binding commitment to that investigators

1. Will not attempt to establish the identity of or attempt to contact any of the included human subjects.
2. Investigators will under no circumstances link these data to Protected Health Information provided to the investigator.
3. Investigators will comply with all relevant rules and regulations imposed by the institution, all national and international laws as well as the legal requirements of the EU General Data Protection Directive (GDP Regulation (EU) 2016/679). This may mean that Investigators need their research to be approved or declared exempt by a committee that oversees research on human subjects, e.g. a local IRB or Ethics Committee. Registration as a Data User requires relevant copies of local approvals being produced.
4. Investigators will acknowledge the use of primary AIMS2TRIALS data and data derived from AIMS-2-TRIALS data, incl. funding through the IMI mechanism, when publicly presenting any results or algorithms that benefitted from their use.
5. Papers, book chapters, books, posters, oral presentations, and all other printed and digital presentations of results derived from AIMS2TRIAL data will contain specific wording in the acknowledgments section that will be agreed with the IMI.
6. Failure to abide by these guidelines will result in termination of my privileges to access AIMS-2-TRIALS data.

Personal Data Privacy Regulation (WP2-6).

Electronic data capture and data integration for research purposes is at the core of the AIMS-2-TRIALS project. Personal privacy legislation is the cornerstone of EU personal data protection, based on the "Data Protection Directive" (DPD) which has been translated into various national privacy legislations in EU. The DPD is also used as a reference for handling sensitive data by non-EU countries.

The main tenets of the DPD for consideration in the AIMS-2-TRIALS project are:

- Data is collected for specified, explicit and legitimate purposes and not to be further processed in a way incompatible with those purposes (art. 6b);
- The collection is adequate, relevant and not excessive in relation to the purposes for which data is collected (art. 6c);
- The collected personal data shall be kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data were collected or for which they are further processed (art. 6e).
- Furthermore, according to art.8a, health data is considered a special (sensitive) data category that can only be disclosed in a very restricted number of situations that include:
- the data subject has given his explicit consent to the processing of those data, except where the laws of the Member State provide that the prohibition may not be lifted by the data subject's giving his consent(art 8.2a);
- data processing is necessary to protect the vital interests of the data subject, or of another person where the data subject is physically or legally incapable of giving his consent (art 8.2c).

Art. 8.3 allows the processing of health data when the data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of healthcare services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy, or by another person also subject to an equivalent obligation of secrecy.

Privacy legislation clearly distinguishes primary and secondary use of data. In most cases, the primary collection of EHR will be done according to art. 8.3 in a diagnostic or therapeutic context. Subsequent use for clinical research will be considered secondary use, and will therefore require informed consent from the data subject and/or de-identification of the data.

In cases where the patient consents to be enrolled in a clinical research study prior to data being collected, the data collection is then considered to be primary and requires the informed consent of the patient.

Regardless of the primary or secondary nature of the collection or processing, researchers should be aware that privacy legislation is not the only reason why the informed consent from the data subject needs to be obtained. Patients may have other ethical objections for participating in a clinical research study, which may be motivated by reasons entirely different than privacy-related.

Hence, the main principles that will be followed for data management in AIMS-2-TRIALS will be de-identification and anonymisation (used in combination with access control of the data, codes of conduct and other procedural regulations for entities handling personal and de-identified data).

The ethical task force stresses that effective electronic data protection is always the result of combining ICT-security (authorised access only to systems and repositories), de-identification and other privacy enhancing technology, and plain organisational

preventive countermeasures (such as codes of conduct for personnel and non-disclosure obligations). Therefore, the EU-AIMS project will establish a clear privacy policy.

All biological samples will be stored and handled in accordance with UK and EU regulations. Most samples will be collected within the European Union. For samples collected in the US, genotyping will be performed in the US (this is ethically approved separately, and we are not seeking approval for this related work that is going to be carried out in the USA) and only electronic data will be shared to comply with the US regulations.

RUMC and IP will establish an informatics platform for safe, secure data storage [113] and deliver end-to-end privacy protection for sensitive data while enabling full data access functionality and implementing the principles of 'data security by design', meeting the legal requirements of the EU General Data Protection Directive (GDP Regulation (EU) 2016/679). The security and access rights procedures will take into account national, and international legislation so as to ensure - with our US and other partners (cf WP6 Task2) - the legal, ethical, and efficient reuse of data by the scientific community. All consortium partners will be required to check against relevant national regulations and ensure compliance, and we will store all relevant declarations centrally. Moreover, we will keep on file (also stored centrally); 1) detailed information on the procedures for data collection, storage, protection, retention, and destruction, and confirmation that they comply with national and EU legislation; 2) evidence that transfer of personal data from/to a non-EU country or international organisation, is authorised and complies with national and EU legislation; and 3) relevant authorisations for further processing of previously collected personal data. All these issues will be specified as part of the grant agreement.

Protection of research participants' confidentiality

The European Guidance for Healthcare Professionals on Confidentiality and Privacy in Healthcare will be respected and all study procedures will follow this guidance. All documents and data will be handled with strict confidentiality. Names and person-related data will be subject to the conditions of the national Protection Acts and European Directives and rules. In the documentation and data analysis phase, the patient-related data will be recorded pseudonymously and will be identifiable only by randomisation number, initials and birth date. The investigating physician will provide the monitor access to the patient file according to the monitoring process (quality control of data recording, archiving of source documents, ensuring that queries are processed immediately and completely, and review of SAE documentation).

The proposed trials will handle data of patients fairly. Data will processed for limited purposes of the studies. Therefore only relevant data will be collected. Data will be processed accurately (see above according to protection acts and monitored according to GCP). Data will be used for the analysis of the results of the proposed trials and will be not kept longer than is needed, but as long as to protect safety of the patients. No data will be transferred to countries without adequate protection.

5.1.3 Animals

We will not carry out any work in non human primates. Moreover, we will keep on file copies of ; 1) relevant authorisations for animal experiments (covering also the work with genetically modified animals); and 2) training certificates/personal licenses of the staff involved in animal experiments. This will be specified in the grant agreement.

This work will be undertaken in laboratories of five academic partners (**UNIBAS, KCL, RG, UEDIN** and **UULM**); and we address the specific issues herein. This research inevitably requires the use of laboratory animals as the key objective of this part of the project which is the study of the genetic and environmental influences on behaviour, the living brain, and the study of brain circuits involved. Since the expected relevant results are caused by complex interactions between cells, tissues and brain areas, the use of alternative methods would not be advisable to achieve the experimental goals. The anticipated benefits of the project justify the use of animals due to the fact that alternative methods are not applicable. We will use genetically modified rodents – to allow specific genetic questions to be addressed and to relate our work in humans (e.g. people with SHANK3 or TSB2 mutations) to rodent models of the disorder. The 3 Rs rule will be strictly applied:

Refinement: minimise suffering and distress. All reasonable steps will be taken to ensure the humane treatment of animals, so as to minimise discomfort, distress and pain. All surgical procedures will be performed under anaesthesia, with good post-operative care. Euthanasia will not be performed in presence of other animals. Animals will be humanely killed at defined end points according to national ethical rules through cervical dislocation or CO2 exposure.

Reduction: minimise number of animals used. For assessing preclinical and translational validity, live mice and rats will have to be used. All partners have developed in depth expertise in animal experimentation and use validated and optimised protocols that will reduce the number of animals needed to obtain significant results. The experimental design has been specifically powered to achieving statistically significant differences using the minimum possible number of animals. Thus, for example, the groups for comparison between treatments and conditions are generally powered to 10 animals to allow paired data comparison using the same animal for controls and tests. Alternative designs based on independent group comparison would require a much larger number of animals, and only be used when paired data comparison are not possible (for example, effects of a given condition in different model mice strains). Web sites as: Dr. [redacted] **http://www.3rs-reduction.co.uk**, or

http://www.biomath.info/ will be used for the experimental design and to estimate the sample size. Also, to implement our standards we will use factorial experimental design to maximize the data collected from each animal. In addition, we will develop a database to register every piece of tissue obtained from these animals, which will be efficiently stored for any refinement of our experiments and for future studies

Replacement: avoid the use of living animals. Replacement: avoid the use of living animals. Mice share 95% of the genes with humans and genes linked to disabilities in cognitive function in humans they also have been demonstrated to cause similar deficits in mice. They are easy to maintain, reproduces quickly, and are very amenable to genetic manipulations and analysis. For all the above reasons, mice are the most appropriate animals for our experiments, as complex CNS behaviour (e.g. EEG, neurophysiological signals related to information processing, social behaviour, learning and memory) can be studied only in intact animals. It is important to mention that, our understanding on the neural circuits function and the consequence of disrupting this circuitry is still very limited. Therefore, it is difficult to built computer models based on what is still unknown. Mice are the most commonly used species to investigate genetic risk factors through gene targeting and drug action on CNS neuronal activity, particularly at neurocircuitry level. This is particularly facilitated by the availability of mouse lines available from repositories for mutations in genetic disease risk factors and cre-recombinase expressing lines that allow for conditional, cell type-specific gene ablation. Nevertheless, where it is possible, we will use in vitro techniques (cell cultures, brain slices) for electrophysiology, because this can reduce the number of living animals used in our experiments. Over the first 18 months we anticipate using 500 mice, and over the five years a total of 2000 mice. Animals will be maintained on a 12-h light/dark cycle (lights on at 07:00 hours) and housed three-four per cage. Food and water will be always freely available. All experimental procedures will be carried out in strict accordance with European Communities Council Directive on “Protection of Animals Used in Experimental and Other Scientific Purposes” and national regulations (Home Office personal and project licenses under UK Animals, Scientific Procedures) 1986 Act. The experimental procedures in use have been already approved by the Institutional Animal Care and Use Committees. Our work is performed according to the European Union regulations (O.J. of E.C. L358/1 18/12/1986) for the use of laboratory animals and the consortium will follow the Council Directive 90/219/EEC on the “Contained use of genetically modified micro-organisms” and is aware of the guidelines given to the European Commission by the “European Group on Ethics in Science and New Technologies” on “Ethical aspects of genetic modification of animals” (Number 7, 21st of May, 1996).

Animal models of cognitive dysfunction that relate to clinical endpoints [WP2]. One of our aims is to improve the predictive validity of animal assays of cognition used for the discovery of drugs capable of addressing the major unmet clinical need of cognitive dysfunction associated with autism. By employing sensitive, translatable tests of cognition it is possible to measure such functions in rodents that appear to be controlled by homologous regions of the human brain. Animal studies are particularly necessary for establishing the possibility of adverse side-effects and the brain location and the causal mechanisms of action of the medication. The behavioural measures cannot be provided by computational modelling, especially as too little is known for accurate computer simulations of the neural control of behaviour. Tissue culture studies hardly reproduce the complex networks in vivo. For example, many of the inputs and therefore, modulation to the cerebral cortex come from subcortical regions or subtypes of neurons (chandelier cells), which will be absent in vitro. More important, tissue cultures cannot capture the complexity of the systems underlying behaviour and brain imaging in humans is limited by its correlational nature and its lack of spatial and temporal resolution.

Current assays will be **refined** by careful dissection of experimental design and statistical analysis, including power analysis, together with assessment of inter-and-intra laboratory reliability and reproducibility across pharmacological standards and experimental manipulations. Animal numbers will be ultimately **reduced** by allowing the industry to focus on those tests thought most likely to; (i) translate to man; (ii) give adequate signal:to:noise to allow drug effects to be seen; (iii) be reproducible across a wide variety of environmental conditions; and (iv) engage the circuitry relevant to the clinical disorder. There will also be focus on obtaining the maximum behavioural information from each animal by further development of software for apparatus control and data capture. By careful integration across work plans, assays, models and drugs will be consistently applied to achieve converging validity through the use of complementary techniques, for example in vivo electrophysiology in WP2. Over the first 18 months we anticipate using 500 mice, and over the five years a total of 1500 mice. For the present we cannot predict a time when the replacement of animals in research of this nature will be feasible. However, we plan to use in most cases rodents as these infra-primate mammals bear some evolutionary relationship to humans in terms of their basic learning and cognitive capacities, as well as in the structure and function of their brains. Thus, the vast majority of studies will be in rodents: mice are necessary for transgenic studies whereas rats are better suited to the study of brain systems involving manipulations of the central nervous system because of their greater size and because much is already known about this species from neuropharmacological and neuropsychological studies.

Research on animal models will be conducted in the countries listed below in accordance with national and international regulations.

EU countries	
Country	*Applicable National Regulation(s)*
Germany	Tierschutzgesetz (TierSchG) (Animal Protection Act) of 18 May 2006 (BGBl. I S. 1206, 1313), last modified 28.07.2014. Contains federal law on the protection of laboratory animals. Gentechnikgesetz (GenTG) (Act on the Regulation of Genetic Engineering) of 16 December 1993 (BGBl. I S. 2066), last modified 07.08.2013. Contains federal law on the handling of genetically modified organisms, including laboratory animals. Inflammation experiments proposed were already approved by the Committee for Animal Experimentation of the University of Ulm and the regional administrative authority in Tübingen (TVA No. 1293).
Netherlands	The GELIFES institute is a research institute of the Faculty of Mathematics and Natural Sciences at the University of Groningen, the Netherlands which is licensed by the Ministry of Economic Affairs to perform animal experiments (license number: 10500). The laboratory animal facility of the Faculty of Mathematics and Natural Sciences meets all legal requirements for housing of and performing experiments with laboratory animals as set out in Annex III of European Directive 2010/63/EU. According to the Dutch Experiments on Animals Act and conform the EU standards (European Directive 2010/63/EU), project proposals (animal experiments) are evaluated by the Animal Ethics Committee (DEC), the Animal Welfare Body (IvD), and the Central Authority for Scientific Procedures on Animals (CCD).
Switzerland	The project involves the use of small laboratory animals (transgenic and non-transgenic). All experimental procedures have been reviewed by the cantonal veterinary office Basel-Stadt, Switzerland and will be performed in compliance with relevant EU and national legislation (Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes).
UK	All experiments described in this proposal have been reviewed by the corresponding local and national committees and approved under Home Office (HO) licenses PPL 70/8331 (Oscar Marín) and PPL 70/8322 (Beatriz Rico), in compliance with relevant UK and EU legislation (Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes).

5.1.4 Non-EU countries

Our research involves South Africa and Canada and they will study local people with and without ASD. Personal data from those individuals will be imported to the EU (including cognitive/behavioural measures, blood and genetic samples, and EEG/MRI data). In turn the researchers in South Africa and Canada will have access to our (anonymised) data. The same ethical standards will be followed in both South Africa, Canada, and Europe. There are no differences between South Africa, Canada and Europe in the risks to the individuals taking part in our research.

We will ensure that; 1) the research conducted outside the EU is legal in at least one EU Member State; 2) details on the materials which will be imported to/exported from the EU will be kept on file; and 3) copies of import/export authorisations, as required by national/EU legislation will be kept on file. We have given detailed information on the measures to minimise the risks to research participants and staff involved in this project that also impact in non EU countries (at pages 143-145).

Extracted DNA will be exported to Canada – and will be subject to all relevant EU data safeguarding legislation.

5.1.5 Environment Protection

We will use of PET imaging to examine the endogenous transmitters in adult patients and normal volunteers. **Infants and children beneath the age of consent will not be included in PET studies.** There are two major concerns with PET imaging – the direct response to the injected radioligand and the possible effects of radiation exposure. The injection of a tracer dose (typically less than 10 micrograms total per subject) of a radioligand has not had any pharmacological effects in nearly 10,000 studies worldwide and it is widely regarded as safe and tolerable – so long as it is done per the standard and well established procedures. Some subjects may experience transient pain and discomfort from blood vessel cannulation – this is clearly specified in the informed consent documents. The studies will meet all current EU requirements as described in the "Guideline to regulations for

radiopharmaceuticals in early phase clinical trials in the EU" [139] and approved by the Radiation Safety Committee of the Karolinska University Hospital. Accordingly, the radiation dose is limited to below 10 mSieverts. For new radioligands dosimetry will be estimated from whole-body PET-measurements in non-human primates and/or rodents (see above).

The work will be approved by the Ethics Committees of UC (Coimbra), KI (Stockholm) and for KCL the national Integrated Research Application System [IRAS] system in the UK. All work will be conducted in full compliance with the Declaration of Helsinki (and Declaration of Madrid when psychiatric patients are included). Subjects will be included after written informed consent. They are covered by the general insurance of the Portugese, Swedish and UK health care systems and free to withdraw their consent without any explanation or further consequences.

Incidental findings such as unexpected brain anomalies will be followed up by appropriate clinical functions at **Karolinska University Hospital** for Swedish volunteers, **Coimbra University Hospital** for those in Portugal, **or Kings College Hospital** for those in the UK. The studies are prospective and will not include collection of previously collected data. All image files and subsequently generated data in the quantitative analyses will be assigned a code. The key will be stored in a locked safe accessible to one person only. The studies will be conducted in compliance with the relevant Portugese, Swedish and UK Biobank Laws to ensure adequate protection of data and privacy.

The PET-center at the KI has over the years conducted about 9000 single PET-measurements on brain neurotransmission markers in human subjects. The PET centre at the **IOP**/**KCL** has conducted approximately 5000 scans per year since opening in 1991 and the MTIC (Hammersmith Hospital) over 30 drug development-related studies in the last 3 years using novel radiolabelled probes. In general the experimental conditions have been tolerated well by the subjects. UC has carried out similar numbers of PET scans.

5.1.6 Dual Use

The research conducted in AIMS-2-TRIALS does not have any potential for military applications.

5.1.7 Misuse

The research conducted in AIMS-2-TRIALS does not have the potential for malevolent/criminal/terrorist abuse.

5.1.8 Other Ethics Issues

There are no other ethics issues currently identified beyond those discussed above.

5.2 Security

• Activities or results raising security issues: (NO)

• 'EU-classified information' as background or results: (NO)