ESTRATTO DELLA SEDUTA DEL 14/01/2008

DELIBERAZIONE del CONSIGLIO DI AMMINISTRAZIONE

n. 1 del 14/01/2008

Oggetto: **Progetto "*ALERT - Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge*" – Approvazione.**

Presenti i consiglieri:
Giovanni Barbagli (Presidente), Allasia Gioachino, Biggeri Annibale, Naldoni Simone, Palumbo Pasquale, Persiani Niccolò

Assenti giustificati i consiglieri:
Biancalani Luigi, Cima Antonio Ettore, Zubbani Angelo Andrea

Sono presenti:
- il Direttore dell'ARS: Dott.ssa Laura Tramonti
- i Coordinatori degli Osservatori dell'ARS: Dott.ssa Eva Buiatti e Dott.ssa Rodella

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Proponente: Presidente

Dirigente Responsabile: Eva Buiatti

Estensore: Daniele Lachi

Pubblicazione su B.U.R.T.: Atto non soggetto a pubblicazione

ALLEGATI n.: 1

Strutture interessate:
OSSERVATORIO DI EPIDEMIOLOGIA
SETTORE RISORSE UMANE E FINANZIARIE

IL CONSIGLIO DI AMMINISTRAZIONE

Vista la legge regionale 24 febbraio 2005, n. 40 (*Disciplina del servizio sanitario regionale*) e successive modifiche ed integrazioni;

Premesso che:

- il 18 dicembre 2006, il Parlamento Europeo e il Consiglio hanno adottato il Settimo Programma Quadro comunitario di ricerca e sviluppo dell'Unione europea per il periodo 2007-2013, il cui obiettivo è quello di incentivare le attività di ricerca e sviluppo in tutte le diverse discipline scientifiche;
- il programma costituisce una parte essenziale della strategia della Comunità Europea in materia di politica della ricerca e mira a tre grandi obiettivi: realizzazione dello Spazio europeo della ricerca, aumento degli investimenti per la ricerca e rafforzamento dell'eccellenza scientifica in Europa;
- nell'ambito del suddetto programma di ricerca, la Commissione Europea ha approvato l'Invito a presentare proposte del "Settimo Programma Quadro" pubblicato sulla Gazzetta Ufficiale dell'U.E. L 412 del 30-12-2006;

Considerato che:

a) nel contesto sopra delineato, l'Osservatorio di Epidemiologia dell'Agenzia, nell'ambito dei programmi di farmacovigilanza, ha manifestato l'intenzione di partecipare al progetto "*ALERT - Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge*" insieme ad altri soggetti di diversi paesi europei, presentando la propria candidatura al soggetto "Coordinatore" del citato progetto e cioè l'Erasmus Medical Center di Rotterdam;
b) il progetto ha lo scopo di sviluppare un sistema che sia in grado di creare, attraverso dati amministrativi, un segnale di allarme più precoce rispetto alla segnalazione spontanea, per l'identificazione di popolazione ad alto rischio di sviluppare reazioni avverse da farmaci;

Preso atto che, in data 20/12/2007, il progetto sopra descritto ha ricevuto la definitiva approvazione da parte della Commissione Europea, di cui al GRANT AGREEMENT N. 215847 (allegato A alla presente deliberazione, unitamente ai suoi sei allegati), quale parte integrante e sostanziale del presente atto;

Rilevato altresì che:

- la durata del progetto è di 42 mesi a decorrere dal 1 febbraio 2008 (*start date of the project*);
- il piano finanziario relativo al progetto di cui trattasi, prevede, nello specifico, risorse a favore dell'Agenzia pari a complessivi € 181.895,00;

Ribadito come l'ARS:

a) per finalità istitutiva, svolge attività di studio e ricerca in materia di epidemiologia;
b) sia in possesso degli strumenti necessari e delle specifiche competenze per collaborare con il soggetto coordinatore e gli altri soggetti coinvolti nella realizzazione del progetto in oggetto;

Richiamato in particolare l'art. 82 bis della citata legge regionale, nel quale si prevede che l'ARS svolge, previa comunicazione al Consiglio regionale e alla Giunta regionale, compatibilmente con i compiti di cui al comma 1, anche attività di consulenza, studio e ricerca a favore delle aziende sanitarie, delle società della salute, degli enti locali, nonché a favore di altri soggetti pubblici o privati;

Preso atto della comunicazione del Presidente, trasmessa al Consiglio e alla Giunta Regionale, circa l'intendimento dell'Agenzia a prestare la propria attività per la realizzazione del progetto in oggetto;

Visto il Regolamento generale di organizzazione dell'ARS adottato con propria deliberazione n. 10 del 02/04/2007, come modificata poi con deliberazioni n. 25 del 29/05/2007 e n. 41 del 12/09/2007, già approvato dalla Giunta regionale in data 8 ottobre 2007 e sul quale il Consiglio regionale nella seduta del 5 dicembre 2007 ha espresso il parere favorevole di competenza;

A voti unanimi

DELIBERA

1. di autorizzare la partecipazione dell'Agenzia alla realizzazione del progetto "*ALERT - Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge*", nell'ambito del "Settimo Programma Quadro" (GUUE L 412 del 30-12-2006) dell'Unione europea per il periodo 2007-2013, in qualità di partner (*beneficiaries*);

2. di dare piena ed intera esecuzione, al "GRANT AGREEMENT N. 215847" (allegato A alla presente deliberazione unitamente ai suoi sei allegati, quale parte integrante e sostanziale del presente atto), sottoscritto dal Presidente dell'ARS, nella sua qualità di rappresentante legale dell'Ente;

3. di prendere atto che:
   a) la durata del progetto è di 42 mesi a decorrere dal 1° febbraio 2008 (*start date of the project*);
   b) il piano finanziario relativo al progetto di cui trattasi, prevede, nello specifico, risorse a favore dell'Agenzia pari a complessivi € 181.895,00;

4. di individuare nel Coordinatore dell'Osservatorio di Epidemiologia, Dott.ssa Eva Buiatti il Responsabile Scientifico del progetto per conto dell'Agenzia;

5. di autorizzare il Direttore dell'ARS all'adozione di tutti gli atti amministrativi nonché di tutte le iniziative necessarie per il perseguimento delle finalità proprie del progetto di cui alla presente deliberazione;

6. di assicurare, ai sensi dell'art. 1 della legge 7 agosto 1990, n. 241 e successive modificazioni, la pubblicità integrale del presente provvedimento mediante:
   a) inserimento nell'instituenda sezione "*Atti amministrativi*" sul sito web dell'ARS (www.arsanita.toscana.it);
   b) affissione all'Albo dei provvedimenti dell'Agenzia;

F.to Il Direttore
D.ssa Laura Tramonti

F.to Il Presidente
Dott. Giovanni Barbagli

copia conforme all'originale
depositato presso la sede A.R.S.
Il Direttore
Laura Tramonti

COMMISSION OF THE EUROPEAN COMMUNITIES

INFORMATION SOCIETY AND MEDIA DIRECTORATE-GENERAL

Information and Communication Technologies

Collaborative Project

ALERT

Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge

Grant Agreement Number 215847

Grant agreement creation date: 04/12/2007 12:22

SEVENTH FRAMEWORK PROGRAMME

GRANT AGREEMENT No 215847

Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge

Collaborative Project

The **European Community** (the "*Community*"), represented by the **Commission of the European Communities** (the "*Commission*"),

of the **one part**,

and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM, established in DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM - THE NETHERLANDS, represented by Mr Huibert Adriaan Pieter POLS, Dean and vice president Executive Board Erasmus MC, or his authorised representative, the *beneficiary* acting as *coordinator* of the *consortium* (the *"coordinator"*), (*"beneficiary n° 1"*),

of the **other part**

HAVE AGREED to the following terms and conditions including those in the following annexes, which form an integral part of this *grant agreement* (the "*grant agreement*").

Annex I	- Description of Work
Annex II	- General conditions
Annex III	- Non applicable
Annex IV	- Form A – Accession of *beneficiaries* to the *grant agreement*
Annex V	- Form B – Request for accession of a new *beneficiary* to the *grant agreement*
Annex VI	- Form C – Financial statement per funding scheme
Annex VII	- Form D – Terms of reference for the certificate on the financial statements and Form E - Terms of reference for the certificate on the methodology

Article 1 – Accession to the *grant agreement* of the other *beneficiaries*

1. The *coordinator* shall endeavour to ensure that each legal entity identified below accedes to this *grant agreement* as a *beneficiary,* assuming the rights and obligations established by the *grant agreement* with effect from the date on which the *grant agreement* enters into force, by signing Form A in three originals, countersigned by the *coordinator.*

- **FUNDACIO IMIM** established in PASSEIG MARITIM 25-29, 08003 BARCELONA - SPAIN, represented by Mr Andreu FORT, Manager, or his authorised representative (*"beneficiary n° 2"*),

- **UNIVERSITAT POMPEU FABRA** established in PLACA DE LA MERCE 10-12, 08002 BARCELONA - SPAIN, represented by Mr JOSEP JOAN MORESO, RECTOR, or his authorised representative (*"beneficiary n° 3"*),

- **UNIVERSIDADE DE AVEIRO** established in CAMPO UNIVERSITARIO DE SANTIAGO, 3800 AVEIRO - PORTUGAL, represented by Mr Francisco VAZ, Vice-Rector, or his authorised representative (*"beneficiary n° 4"*),

- **IRCCS CENTRO NEUROLESI BONINO PULEJO** established in CTR CASAZZA VIA PALERMO SS 113, 98124 MESSINA - ITALY, represented by Mr Raffaele TOMMASINI, General Director, or his authorised representative (*"beneficiary n° 5"*),

- **UNIVERSITE VICTOR SEGALEN BORDEAUX II** established in RUE LEO SAIGNAT 146, 33076 BORDEAUX CEDEX - FRANCE, represented by Mr Bernard BEGAUD, President de l'Université, or his authorised representative (*"beneficiary n° 6"*),

- **LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE** established in KEPPEL STREET, WC1E7HT LONDON - UNITED KINGDOM, represented by Ms Penny IRELAND, Research Contracts Officer, or her authorised representative (*"beneficiary n° 7"*),

- **AARHUS UNIVERSITETSHOSPITAL, AARHUS SYGEHUS** established in NORREBROGADE 44, 8000 AARHUS - DENMARK, represented by Mr Ole THOMSEN, Hospital Director and/or Ms Anne THOMASSEN, Medical Director, or their authorised representative (*"beneficiary n° 8"*),

- **ASTRAZENECA AB** established in , 151 85 SOEDERTAELJE - SWEDEN, represented by Mr Peter MOLDEUS, Vice President, or his authorised representative (*"beneficiary n° 9"*),

- **THE UNIVERSITY OF NOTTINGHAM** established in UNIVERSITY PARK, NG7 2RD NOTTINGHAM - UNITED KINGDOM, represented by Mr Martin WYNNE-JONES, Director of Finance, or his authorised representative (*"beneficiary n° 10"*),

- **UNIVERSITA DEGLI STUDI DI MILANO - BICOCCA** established in PIAZZA DELL'ATENEO NUOVO 1, 20126 MILANO - ITALY, represented by Mr Marcello FONTANESI, Rector, or his authorised representative (*"beneficiary n° 11"*),

- **AGENZIA REGIONALE DI SANITA** established in VIA VITTORIO EMANUELE II 64, 50134 FIRENZE - ITALY, represented by Mr GIOVANNI BARBAGLI, PRESIDENT, or his authorised representative (*"beneficiary n° 12"*),

- **PHARMO COOPERATIE UA** established in PAPENDORPSEWEG 65, 3528BJ UTRECHT - THE NETHERLANDS, represented by Mr Ernst Jan DE GRAAG, Managing Director, or his authorised representative (*"beneficiary n° 13"*),

- **SOCIETA SERVIZI TELEMATICI SRL** established in VIA MEDICI GIACOMO 9/A, 35138 PADOVA - ITALY, represented by Mr Luigi CANTARUTTI, President, or his authorised representative (*"beneficiary n° 14"*),

- **UNIVERSIDADE DE SANTIAGO DE COMPOSTELA** established in PRAZA DO OBRADOIRO S/N, PAZO DE SAN XEROME, 15782 SANTIAGO DE COMPOSTELA - SPAIN, represented by Ms María José ALONSO FERNÁNDEZ, Vicechancellor for Research and Innovation, or her authorised representative (*"beneficiary n° 15"*),

All the *beneficiaries* together form the *consortium (the "consortium")*.

2. The *coordinator* shall send to the *Commission* one duly completed and signed Form A per *beneficiary* at the latest 45 calendar days after the entry into force of the *grant agreement*. The two remaining signed originals shall be kept, one by the *coordinator* to be made available for consultation at the request of any *beneficiary*, and the other by the *beneficiary* concerned.

3. Should any legal entity identified above, fail or refuse to accede to the *grant agreement* within the deadline established in the previous paragraph, the *Commission* is no longer bound by its offer to the said legal entity(ies). The *consortium* may propose to the *Commission*, within the time-limit to be

fixed by the latter, appropriate solutions to ensure the implementation of the *project*. The procedure established in Annex II for amendments to this *grant agreement* will apply.

4. The *beneficiaries* are deemed to have concluded a *consortium agreement* (the "*consortium agreement*") regarding the internal organisation of the *consortium*.

Article 2 – Scope

The *Community* has decided to grant a financial contribution for the implementation of the *project* as specified in Annex I, called **"Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge *(ALERT)*"** (the "*project*") within the framework of the Specific Programme **"Cooperation"** and under the conditions laid down in this *grant agreement*.

Article 3 – Duration and *start date* of the *project*

The duration of the *project* shall be **42** months from **01 February 2008** (hereinafter referred to as the "*start date*").

Article 4 – Reporting periods and language of reports

The *project* is divided into reporting periods of the following duration:

- **P1**: from month **1** to month **12**
- **P2**: from month **13** to month **24**
- **Final**: from month **25** to the last month of the *project*

Any report and deliverable, when appropriate, required by this *grant agreement* shall be in **English.**

Article 5 – Maximum *Community* financial contribution

1. The maximum *Community* financial contribution to the *project* shall be **EUR 4,500,000 (FOUR MILLION FIVE HUNDRED THOUSAND *EURO*)**. The actual *Community* financial contribution shall be calculated in accordance with the provisions of this *grant agreement*.

2. Details of the *Community* financial contribution are contained in Annex I to this *grant agreement* which includes:

- a table of the estimated breakdown of budget and *Community* financial contribution per activity to be carried out by each of the *beneficiaries* under the *project*. *Beneficiaries* are allowed to transfer budget between different activities and between themselves in so far as the work is carried out as foreseen in Annex I.

3. The bank account of the *coordinator* to which all payments of the *Community* financial contribution shall be made is:

Name of account holder:	ERASMUS MC
Name of bank:	ABN AMRO BANK N.V.
Account reference:	NL14ABNA0471436313

Article 6 – *Pre-financing*

A *pre-financing* of **EUR 2,400,000 (TWO MILLION FOUR HUNDRED THOUSAND *EURO*)** shall be paid to the *coordinator* within 45 days following the date of entry into force of this *grant agreement*. The *coordinator* shall distribute the *pre-financing* only to the *beneficiaries* who have acceded to the *grant agreement* and after the minimum number of *beneficiaries* required by the *Rules for Participation* as detailed in the call for proposals to which the *project* is related, have acceded to the *grant agreement*.

Beneficiaries hereby agree that the amount of **EUR 225,000 (TWO HUNDRED TWENTY-FIVE THOUSAND *EURO*)**, corresponding to the *beneficiaries'* contribution to the Guarantee Fund referred to in Article II.20 and representing 5% of the maximum *Community* financial contribution referred to in Article 5.1, is transferred in their name by the *Commission* from the *pre-financing* into the Guarantee Fund. However, *beneficiaries* are deemed to have received the full *pre-financing* referred to in the first indent and will have to justify it in accordance with the *grant agreement*.

Article 7 – Special clauses

The following special clauses apply to this *grant agreement*:

7.1 Special clause n°13 - ETHICAL RULES

1. The *beneficiaries* shall comply with the ethical framework of FP7, all applicable legislation, any relevant future legislation and FP7 specific programmes on "Cooperation", "Ideas", "People", "Capacities" (2007-2013) and "Euratom" (2007-2011). (Council Decisions on the specific programmes: 2006/971/EC on "Cooperation", 2006/972/EC on "Ideas", 2006/973/EC on "People", 2006/974/EC on "Capacities" and 2006/976/Euratom on "Euratom").

2. The *beneficiaries* undertake not to carry out research under this *project* involving any of the following activities:
(a) research activities aiming at human cloning for reproductive purposes,
(b) research activities intended to modify the genetic heritage of human beings which could make such change heritable, and
(c) research activities intended 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.

7.2 Special clause n°15 - ETHICAL REVIEW

1. The *beneficiary(ies)* shall provide the *Commission* with a written confirmation that it has received (a) favourable opinion(s) of the relevant ethics committee(s) and, if applicable, the regulatory approval(s) of the competent national or local authority(ies) in the country in which the research is to be carried out before beginning any *Commission* approved research requiring such opinions or approvals. The copy of the official approval from the relevant national or local ethics committees must also be provided to the *Commission*.

2. The *beneficiary(ies)* shall ensure that, where an ethical review has been carried out by the *Commission*, the research carried out under the *project* fully complies with the following additional requirements resulting from the ethical review:
- Where and when and if Informed Consent has been obtained in all relevant cases, and if not needed justify this clearly for each instance : more generally Ensure all documentation is provided to the EC (eg. lacking any IC or pts);

- To Ensure all data protection issues and regulations are complied with : more specifically insured that the subcontractor Servizi Telematici (PED), providing access to the PEDIANET database, should explain with detail the ethical procedures of data privacy and the methods they are using at the moment .

- Expert advice on ethical issues pertaining to data protection is needed in the *consortium* : so, an independent ethical expert is added;

- Provide a report on the ethics to the EC that ought to be presented in month 3, instead of month 12. Furthermore, a section of ethics should be part of the progress reports submitted to the *Commission*;

- Considering the complexity of the issues that will be dealt with, the management structure should contain an advisor or an advisory group that monitors and addresses ethical issues during the course of the work;

- Explain in detail the existing rules which are in use in each of the involved countries at present. The database concerning Children is even more important, being children a vulnerable target.

7.3 Special clause n°16 - CLINICAL RESEARCH

1. The *beneficiary(ies)* shall provide the *Commission* with a statement confirming that it has received (a) favourable opinion(s) of the relevant ethics committee(s) and, if applicable, the regulatory approval of the competent national authority(ies) in the country concerned before beginning any biomedical research involving human beings.

2. (For biomedical research involving human beings including clinical or other trials) The *Commission* shall never be considered as a sponsor for clinical trials in the sense of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Annex I shall indicate the name(s) of any such sponsor(s).

For trials not covered by Directive 2001/20/EC, Annex I shall indicate the name of the person or organisation that is responsible for the initiation, co-ordination and monitoring of the trial.

7.4 Special clause n°31 - CONTRIBUTION TO THE GUARANTEE FUND

Notwithstanding Article 6, the *pre-financing* referred to therein shall be paid to the *coordinator* in accordance with the following:

- a first instalment of the *pre-financing* of **EUR 2,175,000 (TWO MILLION ONE HUNDRED SEVENTY-FIVE THOUSAND *EURO)*** within 45 days following the date of entry into force of this *grant agreement*,

- a second instalment of the *pre-financing* of **EUR 225,000 (TWO HUNDRED TWENTY-FIVE THOUSAND *EURO)*** to be transferred by the *Commission* in the name of the *beneficiaries* into the Guarantee Fund referred to in Article II.20, once the *Commission* has established the Fund and entrusted its financial management to a depository bank.

Article 8 – Communication

1. Any communication or request concerning the *grant agreement* shall identify the *grant agreement* number, the nature and details of the request or communication and be submitted to the following addresses:

For the *Commission*: Commission of the European Communities
Information Society and Media Directorate-General
B-1049 Brussels
Belgium

For the *coordinator*: Prof. Johan van der Lei
DR. MOLEWATERPLEIN 40/50
3015 GE ROTTERDAM
The Netherlands

2. For information or documents to be transferred by electronic means, the following addresses shall be used:

For the *Commission*: INFSO-ICT-215847@EC.EUROPA.EU

For the *coordinator*: j.vanderlei@erasmusmc.nl

3. In case of refusal of the notification or absence of the recipient, the *beneficiary* or the *consortium*, as the case may be, is deemed to have been notified on the date of the latest delivery, if notification to the *coordinator* has been sent to one of the addresses mentioned in paragraphs 1 and 2 and to their legal representative. Other *beneficiaries* are deemed to have been notified if notification has been sent to the address mentioned in Article 1.1.

4. Any communication or request relating to the processing of personal data (Article II.13) shall be submitted, using the address(es) for the *Commission* identified in paragraphs 1 and 2, to the Controller responsible for the processing: Head of *IST Operations* Unit.

Article 9 – Applicable law and competent court

The *Community* financial contribution is a contribution from the *Community* research budget with the aim to implement the 7th Research Framework Programme (FP7) and it is incumbent on the *Commission* to execute FP7. Accordingly, this *grant agreement* shall be governed by the terms of this *grant agreement*, the *Community* acts related to FP7, the Financial Regulation applicable to the general budget and its implementing rules and other *Community* law and, on a subsidiary basis, by the law of Belgium.

Furthermore, the *beneficiary* is aware, and agrees, that the *Commission* may take a decision to impose pecuniary obligations, which shall be enforceable in accordance with Article 256 of the Treaty establishing the European Community and Articles 164 and 192 of the Treaty establishing the European Atomic Energy Community.

Notwithstanding the *Commission*'s right to directly adopt the recovery decisions referred to in the previous paragraph, the Court of First Instance, or on appeal, the Court of Justice of the European Communities, shall have sole jurisdiction to hear any dispute between the *Community* and any *beneficiary* concerning the interpretation, application or validity of this *grant agreement* and the validity of the decision mentioned in the second paragraph.

Article 10 – Application of the *grant agreement* provisions

Any provision of this part of the *grant agreement*, shall take precedence over the provisions of any of the Annexes. The provisions of Annex III shall take precedence over the provisions of Annex II, and both shall take precedence over the provisions of Annex I.

The special clauses set out in Article 7 shall take precedence over any other provisions of this *grant agreement*.

Article 11 – Entry into force of the *grant agreement*

This *grant agreement* shall enter into force after its signature by the *coordinator* and the *Commission*, on the day of the last signature.

Done in two originals in **English.**

For the *coordinator* done at: Rotterdam - NL

Name of the legal entity: Erasmus University Medical Centrum Rotterdam

Name of legal representative: Prof dr. H.A.P. Pols, Vice-president and Dean

Stamp of the organisation (if applicable):

Signature of legal representative:

Date: 14.12.2007

For the *Commission* done at Brussels:

Name of legal representative: R.F. de Bruïne
Authorised Representative of
~~Fabio~~ Colasanti
General Director

Signature of legal representative:

Date: 20 DEC. 2007

SEVENTH FRAMEWORK PROGRAMME
THEME 3
ICT - Information and Communication Technologies

Grant agreement for: **Collaborative Project**
Small or medium-scale focused research project

Annex I - "Description of Work"

Project acronym: *ALERT*
Project full title: *Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge*

Grant agreement no.: *215847*

Date of preparation of Annex I (latest version): 24/10/2007
Date of approval of Annex I by Commission: *03/12/2007*

Table of Contents

A1. Budget breakdown and project summary

A.1 Overall budget breakdown for the project

Grant agreement Preparation Forms

EUROPEAN COMMISSION

7th Framework Programme on Research, Technological Development and Demonstration

Collaborative Project

A3.2: What it costs

Proposal number (1)	215847	*Proposal acronym (2)*	ALERT

ONE FORM PER PROJECT

Participant number in this project	Organisation short name	Estimated eligible costs (whole duration of the project)				TOTAL A+B+C+D	Total receipts	Requested EC contribution
		RTD / Innovation (A)	Demonstration (B)	Management (C)	Other (D)			
1	EMC	1.040.846,00	0,00	43.512,00	118.192,00	1.202.550,00	0,00	942.338,00
2	FIMIM	43.128,00	0,00	284.421,00	80.092,00	407.641,00	0,00	396.859,00
3	UPF	534.728,00	0,00	18.470,00	6.035,00	559.233,00	0,00	425.551,00
4	UAVR	347.360,00	0,00	19.214,00	6.916,00	373.490,00	0,00	286.650,00
5	NEUROLESI	506.795,00	0,00	19.352,00	12.003,00	538.150,00	0,00	411.451,00
6	UB2	334.756,00	0,00	23.057,00	15.676,00	373.489,00	0,00	289.800,00
7	LSHTM	251.235,00	0,00	0,00	8.672,00	259.907,00	0,00	197.098,00
8	AUH-AS	227.408,00	0,00	0,00	6.278,00	233.686,00	0,00	176.834,00
9	AZ	392.466,00	0,00	0,00	23.883,00	416.349,00	0,00	220.116,00
10	UNOTT	391.624,00	0,00	0,00	14.929,00	406.553,00	0,00	308.647,00
11	UNIMIB	226.760,00	0,00	0,00	11.825,00	238.585,00	0,00	181.895,00
12	ARS	226.760,00	0,00	0,00	11.825,00	238.585,00	0,00	181.895,00
13	PHARMO	226.067,00	0,00	0,00	10.275,00	236.342,00	0,00	179.825,00
14	PEDIANET	226.067,00	0,00	0,00	10.275,00	236.342,00	0,00	179.825,00
15	USC	153.926,00	0,00	0,00	5.772,00	159.698,00	0,00	121.216,00
TOTAL		**5.129.926,00**	**0,00**	**408.026,00**	**342.648,00**	**5.880.600,00**	**0,00**	**4.500.000,00**

A.2 Project summary

Grant agreement Preparation Forms

EUROPEAN COMMISSION

7th Framework Programme on Research, Technological Development and Demonstration

Collaborative Project

A1: Our Project

Project number (1)	215847	*Project acronym (2)*	ALERT

ONE FORM PER PROJECT

GENERAL INFORMATION

Project Title (3)	Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge		
Starting Date (4)	01/02/2008		
Duration in months (5)	42	*Call (part) identifier (6)*	FP7-ICT-2007-1
Activity code(s) most relevant to your topic (7)	ICT-1-5.2	-	-
Free keywords (8)	Electronic patient records, Patient safety, Adverse drug event, Pharmacovigilance, Data mining		

Abstract(9) (max. 2000 char.)

Serious adverse effects resulting from the treatment with thalidomide prompted modern drug legislation more than 40 years ago. Post-marketing spontaneous reporting systems for suspected adverse drug reactions (ADRs) have been a cornerstone to detect safety signals in pharmacovigilance. It has become evident that adverse effects of drugs may be detected too late, when millions of persons have already been exposed.

In this project, an alternative approach for the detection of ADR signals will be developed. Rather than relying on the physician's capability and willingness to recognize and report suspected ADRs, the system will systematically calculate the occurrence of disease (potentially ADRs) during specific drug use based on data available in electronic patient records. In this project, electronic health records (EHRs) of over 30 million patients from several European countries will be available. In an environment where rapid signal detection is feasible, rapid signal assessment is equally important. To rapidly assess signals, a number of resources will be used to substantiate the signals: causal reasoning based on information in the EHRs, semantic mining of the biomedical literature, and computational analysis of biological and chemical information (drugs, targets, anti-targets, SNPs, pathways, etc.).

The overall objective of this project is the design, development and validation of a computerized system that exploits data from electronic healthcare records and biomedical databases for the early detection of adverse drug reactions. The ALERT system will generate signals using data and text mining, epidemiological and other computational techniques, and subsequently substantiate these signals in the light of current knowledge of biological mechanisms and in silico prediction capabilities. The system should be able to detect signals better and faster than spontaneous reporting systems and should allow for identification of subpopulations at higher risk for ADRs.

A.3 List of beneficiaries

List of Beneficiaries

Beneficiary Number	Beneficiary name	Beneficiary short name	Country	Date enter project	Date exit project
1 (Coordinator)	Erasmus Universitair Medisch Centrum Rotterdam	EMC	Netherlands	Month 1	Month 42
2	Fundació IMIM	FIMIM	Spain	Month 1	Month 42
3	Universitat Pompeu Fabra	UPF	Spain	Month 1	Month 42
4	Universidade de Aveiro	UAVR	Portugal	Month 1	Month 42
5	IRCCS Centro Neurolesi Bonino Pulejo	NEUROLESI	Italy	Month 1	Month 42
6	Université Victor Segalen Bordeaux II	UB2	France	Month 1	Month 42
7	London School of Hygiene and Tropical Medicine	LSHTM	UK	Month 1	Month 42
8	Aarhus Universitet Hospital, Aarhus Sygehus	AUH-AS	Denmark	Month 1	Month 42
9	AstraZeneca AB	AZ	Sweden	Month 1	Month 42
10	The University of Nottingham	UNOTT	UK	Month 1	Month 42
11	Univesità degli Studi di Milano-Bicocca	UNIMIB	Italy	Month 1	Month 42
12	Agenzia Regionale di Sanità	ARS	Italy	Month 1	Month 42
13	PHARMO Cooperatie U.A.	PHARMO	Netherlands	Month 1	Month 42
14	Societa' Servizi Telematici SRL	PEDIANET	Italy	Month 1	Month 42
15	Universidade de Santiago de Compostela	USC	Spain	Month 1	Month 42

B1. Concept and objectives, progress beyond state-of-the-art, S/T methodology and work plan

B 1.1 Concept and project objective(s)

Serious adverse effects resulting from the treatment with thalidomide prompted modern drug legislation more than 40 years ago.[1] During that period, the mainstay of drug safety surveillance has been the collection of spontaneous Adverse Drug Reactions (ADRs).[2,3] The current and future challenges of drug development and drug utilization, and a number of recent high-impact drug safety issues (e.g. rofecoxib (Vioxx) and SSRIs) require re-thinking of the way safety monitoring is conducted.[4] It has become evident that adverse effects of drugs may be detected too late, when millions of persons have already been exposed. The need to change drug safety monitoring is underlined in the current public consultation about the future of pharmacovigilance in the EU.[5]

Pharmacovigilance is the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities. The timely discovery of unknown or unexpected ADRs is one of its major challenges, because most of the drugs enter the market with less than 3000 exposed subjects, implying that reactions occurring with rates lower than 1/1000 could easily remain undetected for long periods of time. Post-marketing spontaneous reporting systems for suspected ADRs have been a cornerstone to detect safety signals in pharmacovigilance.[6] Although many ADRs were detected by spontaneous reporting systems, these systems have inherent limitations that hamper signal detection.[7] The major weakness is that these systems depend entirely on the ability of a physician to, first, recognize an adverse event as being related to the drug. Subsequently, the physician needs to actually report the case to the local spontaneous reporting database. The greatest limitations, therefore, are under-reporting and biases due to selective reporting.[8] Investigations have shown that the percentage of ADRs being reported varies between 1 and 10%.[9,10,11] These problems may lead

[1] Mann RD, Andrews EB, editors. Pharmacovigilance. Chichester: John Wiley & Sons; 2002, p 3-10.
[2] Olsson S. The role of the WHO programme on International Drug Monitoring in coordinating worldwide drug safety efforts. Drug Saf 1998; 19: 1-10.
[3] Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. J Gen Intern Med 2003;1 8: 57-60.
[4] Avorn J. Evaluating drug effects in the post-Vioxx world: there must be a better way. Circulation 2006; 113: 2173-6.
[5] http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.
[6] Rodriguez EM, Staffa JA, Graham DJ. The role of databases in drug postmarketing surveillance. Pharmacoepidemiol Drug Saf 2001; 10: 407-10.
[7] Meyboom RH, Egberts AC, Edwards IR, Hekster YA, de Koning FH, Gribnau FW. Principles of signal detection in pharmacovigilance. Drug Saf 1997; 16: 355-65.
[8] Belton KJ. Attitude survey of adverse drug-reaction reporting by health care professionals across the European Union. The European Pharmacovigilance Research Group. Eur J Clin Pharmacol 1997; 52: 423-7.
[9] Alvarez-Requejo A, Carvajal A, Begaud B, Moride Y, Vega T, Arias LH. Under-reporting of adverse drug reactions. Estimate based on a spontaneous reporting scheme and a sentinel system. Eur J Clin Pharmacol 1998; 54: 483-8.
[10] Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BH. Attitudinal survey of voluntary reporting of adverse drug reactions. Br J Clin Pharmacol 1999; 48: 623-7.
[11] De Bruin ML, van Puijenbroek EP, Egberts AC, Hoes AW, Leufkens HG. Non-sedating antihistamine drugs and cardiac arrhythmias -- biased risk estimates from spontaneous reporting systems? Br J Clin Pharmacol 2002; 53: 370-4.

to underestimation of the significance of a particular reaction and delay in signal detection, as well as spurious detections.[12]

In this project, an alternative approach towards the detection of ADR signals will be developed with the objective of overcoming the shortcomings of spontaneous reporting databases and providing a solid basis for large-scale monitoring of drug safety. Rather than relying on the physician's capability and willingness to recognize and report suspected ADRs, the system will systematically calculate the occurrence of disease (potentially ADRs) during specific drug use based on data (time-stamped exposure and morbidity data) available in electronic patient records. Europe plays a leading role in the development and use of electronic patient records.[13,14] As a result, a number of European Electronic Healthcare Record (EHR) databases are available. Appropriate monitoring and use of these databases has an enormous potential for earlier detection of ADR signals.[15,16] In this Consortium, anonymous records of over 30 million Europeans will be used for early detection of ADR signals.

The ability to generate signals must be accompanied by the ability to further assess or substantiate these signals. In an environment where rapid signal detection is feasible, rapid signal assessment is equally important. To rapidly assess signals, a number of resources are available: causal reasoning based on information in the EHR, semantic mining of the literature, and computational analysis of pharmacological and biological information (drugs, targets, anti-targets, SNPs, pathways, etc.). These resources allow us, in principle, to put a signal in the context of our current biomedical knowledge.

Both the underlying patient data (e.g. the number of people using a given drug increases, or the indication domain of a drug changes) and our biological understanding evolve over time. Consequently, both signal generation and assessment have to be viewed as a continuous process. As a result, any monitoring system should be able to re-assess previous conclusions in the light of new data or evidence. With optimal use of ICT both in generating and assessing signals, an automated system for detection, substantiation and re-assessment should be feasible.

The overall objective of the ALERT project **is the design, development and validation of a *computerized system* that exploits data from *electronic healthcare records* and *biomedical databases* for the *early detection of adverse drug reactions.*** The ALERT system will *generate signals* using data mining, epidemiological, computational and text mining techniques, and subsequently *substantiate these signals* in the light of *current knowledge and understanding of biological mechanisms*. The system should be able to detect signals better and faster than spontaneous reporting systems and should allow for identification of subpopulations at higher risk for ADRs. For the system to operate as an adjunct to safety reviewers during signal evaluation and follow-up, it will enable easy access to the underlying data sources, allowing to quickly focus on information that is pertinent to a suspected ADR.

[12] Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997; 17: 374-89.
[13] Ash JS, Bates DW. Factors and forces affecting EHR system adoption: report of a 2004 ACMI discussion. J Am Med Inform Assoc 2005; 12: 8-12.
[14] Schade CP, Sullivan FM, de Lusignan S, Madeley J. e-Prescribing, efficiency, quality: lessons from the computerization of UK family practice. J Am Med Inform Assoc 2006; 13: 470-5.
[15] McClellan M. Drug safety reform at the FDA—pendulum swing or systematic improvement? NEJM 2007; 356: 1700-2.
[16] Platt R. The future of drug safety: challenges for FDA. Presented at the Institute of Medicine Forum. Washington DC. March 12, 2007.

In this project, electronic healthcare records comprising demographics, drug use and clinical data of over 30 million patients from several European countries will be available. As shown in *Figure 1*, these EHR databases form the foundation of the project, insofar as they supply the patient data on top of which the system is built. Special attention will be given to patient groups that are not routinely involved in clinical trials, for ethical or practical reasons (e.g. pregnant women, elderly people, people using many drugs simultaneously, and children). In particular in children there is an increased need for post-marketing surveillance.[17,18] We therefore included in the project a database exclusively devoted to pediatric data (PEDIANET, Italy).[19] PEDIANET, together with data from general practice in other databases, will provide ample representation of children in our data set.

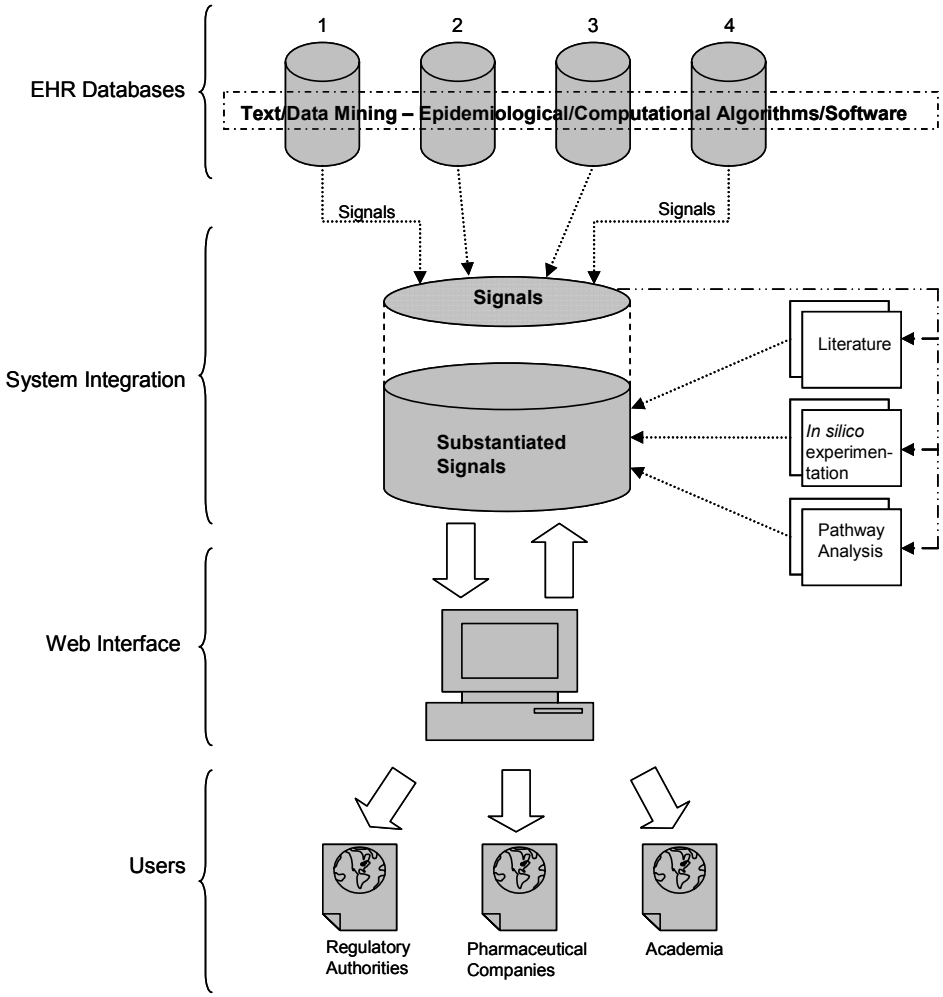


Figure 1: Overview of the ALERT system working flow.

[17] Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. Pediatrics 2006; 118: 555-62.

[18] Iyasu S, Murphy MD. Pharmacovigilance in pediatrics. In: Mann RD, Andrews EB, editors. Pharmacovigilance. Chichester: John Wiley & Sons; 2007. p. 497-506.

[19] Sturkenboom M, Nicolosi A, Cantarutti L, Mannino S, Picelli G, Scamarcia A, Giaquinto C. Incidence of mucocutaneous reactions in children treated with niflumic acid, other nonsteroidal antiinflammatory drugs, or nonopioid analgesics. Pediatrics 2005; 116: e26-33.

A number of designs and techniques will be used to process these electronic medical records. One of the objectives of this project is to study and compare a number of different techniques that, in essence, all aim to detect unexpected or disproportional rates of events. The algorithms that we will study originate not only from the field of (pharmaco)epidemiology, but also from fields such as bio-terrorism, machine learning, and "classical" signal detection.

Once generated, the signals will be substantiated by applying causality criteria (biological plausibility, known reactions). The purpose of this substantiation process is to place the signals in the context of the current biomedical knowledge that might explain the signal. Essentially, we are searching for evidence that supports causal inference of the signal. The list of signals will be assessed by automatically investigating feasible paths connecting the drug and the adverse reaction involved in the signal. The general strategy is the automatic linkage of biomedical entities (drugs, proteins and their genetic variants, biological pathways, and clinical events) by means of data mining approaches and *in silico* predictions based on biomolecular structures.[20] The biological annotations of the drug involved in the signal will be expanded by automatically detecting its metabolites and other molecules showing similar pharmacophoric patterns.[21] To detect associations between these biomedical entities, data and text mining techniques will be used on pharmacological repositories and biomedical literature.[22,23,24] Proteins interacting with the drug or related molecules will be mapped into biological pathways that could be involved in the clinical event that is part of the signal. Information about the human genome variations that affects the proteins of the considered pathways will also be used.

The substantiation process should be largely automated, not only in view of the number of signals to be checked, but also to accommodate the rapid expansion of information in the biomolecular field, as changes in the information sources (e.g. our understanding of certain pathways) may also impact on the assessment of a signal. As changes of the information sources occur frequently, the process of re-evaluating the signals must be largely automatic in order to be tractable.

The signal detection and substantiation algorithms will be integrated in a computerized ADR detection and monitoring system. This involves the development of an evidence weighting scheme to combine the various pieces of information and present the user with a final list of ranked signals. Although the detection and substantiation process will be automatic, the information used by the system should be easily accessible to facilitate the signal evaluation process. Through a web interface, safety reviewers should be able to quickly inspect the underlying EHR data, relevant literature, and pertinent information from any other data source that was used to generate the signals. The system will allow for regular monitoring of signal strengths over time, to facilitate safety reviewers in deciding which signals should be further explored. The system is envisaged to be a primary tool for use by regulatory authorities, but it should also be of interest to pharmaceutical companies and academic institutes, providing a common platform for detection and understanding of adverse drug reactions.

[20] Farahani P, Levine M. Pharmacovigilance in a genomic era. The Pharmacogenomics Journal 2006; 6: 158-61.
[21] Boyer S, Zamora I. New methods in predictive metabolism. Mol Divers 2002; 5: 277-87.
[22] Erhardt RAA, Schneider R, Blaschke C. Status of text-mining techniques applied to biomedical text. Drug Disc Today 2006; 11: 315-25.
[23] Garcelon N, Mougin F, Bousquet C, Burgun A. Evidence in pharmacovigilance: extracting adverse drug reactions articles from MEDLINE to link them to case databases. Stud Health Technol Inform 2006; 124: 528-33.
[24] Banville DL. Mining chemical structural information from the drug literature. Drug Disc Today 2006; 11: 35-42.

As mentioned above, the ultimate aim of this proposal is to develop an innovative system for the early detection of adverse drug reactions. In order to assess whether that claim is met, *validation* is an integral part of this project. The system will be tested retrospectively using test sets that are based on recent literature, including both known side effects and spurious signals. The system's ability to rediscover drug-event combinations from the test set with known side effects will provide an indication of the sensitivity of the system. The system's ability not to signal drug-event combinations from the test set with spurious signals will provide an indication of the specificity of the system.

After the system has been validated retrospectively, a prospective evaluation will be done by further investigating the top-ranking signals generated by the system. For the verification of these top-ranking signals, traditional hypothesis testing approaches, including pharmaco-epidemiological studies, will be followed.

The ultimate objective of the proposed project is to demonstrate that an earlier detection of adverse side effects of drugs is possible using electronic healthcare records.[15] The *single most important quantifiable outcome,* therefore, is the demonstration that earlier detection is indeed possible. As already mentioned, for this purpose we will aim to demonstrate that we could have detected recently discovered side effects earlier (for example, in retrospect we would have significantly reduced the lag-time for discovering the Vioxx issue). This will be complemented with the analysis of new signals, which will provide a further quantifiable outcome.

B 1.2 Progress beyond the state of the art

As mentioned in section B1.1 above, the collection of post-marketing, spontaneous reports of suspected adverse drug reactions has been so far the main pillar of drug safety surveillance. Although several initiatives of the Council for International Organizations of Medical Sciences (CIOMS) and International Conference on Harmonization (ICH) have added guidance on the collection, evaluation and reporting of safety data,[25] progress has to be made in the development of more robust methodologies for monitoring drug safety.[5,26] This view is shared by the European Medicines Evaluation Agency, which has asked for a public consultation on the future of pharmacovigilance in Europe.[27]

Spontaneous reporting systems have inherent limitations that hamper signal detection, both by traditional and automated methods.[28,29] In this project, a new approach towards the detection of ADR signals will be developed. It will help to overcome the 'reporting bias' and underreporting of physicians, and it will more efficiently use clinical data that are already available in electronic format. The solution is based on automatically exploiting the data stored in large EHR systems. So far, electronic health care databases have been used only for hypothesis testing and not for systematic monitoring of drug exposure and event rates, an approach that could lead to efficient and unbiased signal generation. A good example of what

[25] Tsintis P, La Mache E. CIOMS and ICH initiatives in pharmacovigilance and risk management: overview and implications. Drug Saf 2004; 27: 509-17.
[26] The future of drug safety: promoting and protecting the health of the public. Washington, DC: Institute of Medicine; 2006.
[27] http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/icr.htm.
[28] Almenoff J, Tonning JM, Gould AL, Szarfman A, Hauben M, Ouellet-Hellstrom R, Ball R, Hornbuckle K, Walsh L, Yee C, Sacks ST, Yuen N, Patadia V, Blum M, Johnston M, Gerrits C, Seifert H, Lacroix K. Perspectives on the use of data mining in pharmaco-vigilance. Drug Saf 2005; 28: 981-1007.
[29] Hauben M, Patadia V, Gerrits C, Walsh L, Reich L. Data mining in pharmacovigilance: the need for a balanced perspective. Drug Saf 2005; 28: 835-42.

databases may add to evidence development in the field of drug safety is the case of Vioxx (rofecoxib). Soon after the first signal was generated, more than 15 studies were conducted together including more than 60,000 cases of myocardial infarction and 1500 exposed cases.

In Europe, the introduction of electronic healthcare records has, albeit with significant differences between Member States, seen a steady growth over the past years. In some countries, whole segments of the healthcare delivery system rely on electronic records (e.g. primary healthcare in the UK or The Netherlands).[13] Compared to other developed areas, Europe is playing a leading role in the use of electronic healthcare records.[30] For monitoring of adverse events, very large populations need to be followed up to achieve early detection of disproportional event rates with specific drugs. New drugs, for example, may slowly penetrate the market, thereby requiring a large amount of patient data in order to comprise a significant user population. Recently, a number of calculations on required population size have been performed based on newly discovered side effects. It took *five years* for rofecoxib to be withdrawn from the market.[31] Using actual penetration of rofecoxib in the market, it has been calculated that if the medical records of 100 million patients would have been available for safety monitoring, the adverse cardiovascular effect would have been *discovered in just three months*.[15,16]

In Europe, however, the application of ICT in healthcare is fragmented. There is no obvious method to combine different electronic medical records from different locations into a uniform repository. Considering the size of the populations required for early detection of adverse drug events, however, pooling of data is mandatory. The *first area of progress* beyond the current-state-of-the-art that ALERT will induce is *the federation of different databases* of electronic medical records, creating for the first time a *resource of unprecedented size for monitoring of adverse events*. In this project, eight different databases containing medical records of, in total, more than 30 million European citizens, will join forces. The databases stem from different European countries: IPCI (Netherlands), PHARMO (Netherlands), QRESEARCH (UK), the AUHD database (Denmark), the Regional health databases of Lombardy and Tuscany (Italy), Health Search (Italy), and PEDIANET (Italy). IPCI, Health Search, and QRESEARCH are primary care databases, containing routinely collected data on both adults and children. PEDIANET contains data exclusively on children. PHARMO is a comprehensive database of drug prescription data, which has been linked with primary care data as well as hospital data. AUHD and the regional databases in Lombardy and Tuscany are population-based databases of dispensed drugs that can be linked to hospitalizations, death records and laboratory data. *The shared objective of all these databases is to work together towards early detection of adverse drug-related events.* The main characteristics of these databases are summarized in Table 1 (see below).

It is important to note that the information in Table 1 represents a "lower boundary" of available data; *only data that are already available at the start of the project have been listed*. It is also important to note that all of these databases are *currently already used for pharmacovigilance* (albeit for signal *verification* rather than signal *detection*). As a result, all of these databases have a rich publication history and a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy protection are adhered to. From the project's perspective, this is major advantage: the ethical and legal procedures that are required when patient data are used to investigate side effects are

[30] Sturkenboom MCJM. Other European databases for pharmacoepidemiology. In: Mann RD, Andrews EB, editors. Pharmacovigilance. Chichester: John Wiley & Sons, 2007.

[31] Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004; 364: 2021-9.

already in place. In this proposal, we will study how all these different databases have implemented their ethical framework and have translated this to various procedures.

Although we are starting this project with 30 million records in eight databases, which is deemed to be more than sufficient for the purposes of ALERT, a growth in the number of participating databases is envisioned in the long term. This means that the project developments need to enforce an open framework that allows other databases to join in at a later stage. As the project unfolds, the wish of other databases to join the ALERT system will be viewed as an additional indicator of the success of this project.

Fragmentation can also be seen as diversity; and diversity constitutes an opportunity. Researchers in, for example, statistical pattern recognition have long recognized that variety in environments can be translated into variety of learning and testing sets and may result in better understanding of underlying patterns. The *second area of progress,* therefore, will be the *exploitation of this European diversity for routine drug monitoring.*

Mining large datasets in order to discover patterns has a long history. A number of methods have been specifically developed for monitoring side effects of drugs based on spontaneous reporting data,[32,33,34] but the number of fields that could contribute methodology to mine EHR data is much larger and include methods developed to monitor for epidemic diseases[35] (e.g. flu or malaria), bio-terrorism[36,37] (e.g. an attack with an infectious agent), "classical signal analysis" (e.g. the detection of abnormal events in a neonatal intensive care unit[38]), and the general domain of "machine learning".[39,40] Having access to data of more than 30 million individuals will provide an opportunity to test and compare these different algorithms and methods on a scale hitherto not possible. The *third area of progress*, therefore, will be *evaluation on a realistic scale* (that is, involving a population of millions of patients across different databases) of a number of *data mining techniques*. We believe that further development of these techniques constitutes a significant scientific contribution to the methodology of data mining.

To contain the number of spurious (false-positive) detections, several approaches will be followed, including causal reasoning based on information in the EHR, semantic mining of the literature, and the automatic use of information in biological (targets, anti-targets, pathways) and chemical/drug databases. The issue of reducing spurious signals is, from our

[32] Hauben M, Zhou X. Quantitative methods in pharmacovigilance: focus on signal detection. Drug Saf 2003; 26: 159-86.
[33] Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol 2004; 57: 127-34.
[34] Hauben M, Madigan D, Gerrits CM, Walsh L, Van Puijenbroek EP. The role of data mining in pharmacovigilance. Expert Opin Drug Saf 2005; 4: 929-48.
[35] Lober WB, Trigg LJ, Karras BT, Bliss D, Ciliberti J, Stewart L, Duchin JS. Syndromic surveillance using automated collection of computerized discharge diagnoses. J Urban Health 2003; 80: i97-106.
[36] Lober WB, Karras BT, Wagner MM, Overhage JM, Davidson AJ, Fraser H, Trigg LJ, Mandl KD, Espino JU, Tsui FC. Roundtable on bioterrorism detection: information system-based surveillance. J Am Med Inform Assoc 2002; 9: 105-15.
[37] Lombardo J, Burkom H, Elbert E, Magruder S, Lewis SH, Loschen W, Sari J, Sniegoski C, Wojcik R, Pavlin J. A systems overview of the Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE II). J Urban Health 2003; 80: i32-42.
[38] Greene BR, Boylan GB, Reilly RB, de Chazal P, Connolly S. Combination of EEG and ECG for improved automatic neonatal seizure detection. Clin Neurophysiol 2007.
[39] Mitchell TM. Machine learning. Singapore: McGraw-Hill; 1997.
[40] Witten IH, Frank E. Data mining: practical machine learning tools and techniques. San Francisco: Morgan Kaufmann; 2005.

perspective, a hitherto undervalued issue.[41] Spurious signals constitute a significant risk. From the public health perspective, spurious signals may result in withdrawal of effective drugs. Literature documents the impact that such a false alarm can have on public health. In principle, the negative impact of spurious signals may well outweigh the benefit of earlier detection of a true adverse event. Therefore, the benefit of early detection must be balanced with unnecessary concern about spurious signals. From a regulatory perspective, the risk of spurious signals is considerable: it may overwhelm our ability to review and regulate the consequences of these signals. Finally, from a commercial perspective, it is hard to underestimate the consequences of a false alarm. History shows that, even when a drug is cleared from suspicion, the impact on the drug's reputation often cannot be undone. The *fourth area of progress,* therefore*,* will be the *automated exploitation of heterogeneous sources of information to reduce the number of spurious signals.*

Spurious signals have significant consequences. Sertindole, a new atypical neuroleptic known to prolong the QT interval, was suspended in November 1998 because the proportion of reports of fatal reactions suggesting arrhythmia among all reports with sertindole was almost ten (!) times higher than that for other atypical neuroleptics in the UK. This excess risk was not predicted in preclinical data and had not been found in pre-marketing trials. Further studies showed that there was no indication of an actual increase of risk of all causes or cardiac deaths during sertindole treatment, but only an increased risk of it being reported. Three years later, October 2001, the suspension of sertindole was rescinded by the Committee on Proprietary Medicinal Products (CPMP).[42]

These various data sources will be integrated in a computerized signal detection and monitoring system that produces a prioritized list of signals. The system should be able to detect signals better and faster than spontaneous reporting systems, and it should be able to identify subpopulations at higher risk for ADRs. Special attention will be given to the detection of adverse events in *children* (with a database devoted solely to children in the lead) and other at risk groups such as *elderly* and patients with certain co-morbidities. The *fifth area of progress*, therefore, will be a *novel system* that, compared with spontaneous reporting systems, provides the capability for *earlier discovery of ADRs*.

Spontaneous reports may detect adverse effects only after millions of persons have been exposed. Rofecoxib (Vioxx) was withdrawn from the market by the marketing authorisation holder. It took 5 years after its approval before the drug was withdrawn. The relative risk of the association between rofecoxib and myocardial infarction is between 1.5 and 2. Researchers have argued that, if the electronic patient records of 100 million people would have been available for continuous monitoring for adverse drug events, the signal would have been detected in just 3 months.[16]

[41] Chan KA, Hauben M. Signal detection in pharmacovigilance: empirical evaluation of data mining tools. Pharmacoepidemiol Drug Saf 2005; 14: 597-9.

[42] Moore N, Hall G, Sturkenboom M, Mann R, Lagnaoui R, Begaud B. Biases affecting the proportional reporting ratio (PRR) in spontaneous reports pharmacovigilance databases: the example of sertindole. Pharmacoepidemiol Drug Saf 2003; 12: 271-81.

Overall, ALERT is intended to signify a quantum leap forward in comparison with current ADR detection systems. It will develop and use advanced ICT technologies for demonstrating new ways to feasibly exploit the existing wealth of clinical and biomedical data sources for better and faster detection of ADRs. By coupling these results with an open vocation and active dissemination and exploitation studies, ALERT aims at creating a major impact in the field.

Table 1: EHR database characteristics

CHARACTERISTICS	**Pedianet** (Italy)	**Health Search** (Italy)	**Lombardy Regional SISR data** (Italy)	**Tuscany Regional SISR data** (Italy)	**IPCI** (Netherlands)	**PHARMO** (Netherlands)	**QRESEARCH** (UK)	**Aarhus University Hospital DB** (DK)
Current source population	160,000 children	900,000	9,000,000	3,500,000	1,000,000	3,000,000	10,000,000	1,800,000
Demographics								
Unique identifier for linking of files	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Registration date	Yes	Yes	Yes	Yes	Yes	No (based on first prescription)	Yes	Yes
Date of transferring out	Yes	Yes	Yes	Yes	Yes	No (based on last prescription)	Yes	Yes
Date of death	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Date of birth	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gender	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Race	Yes	No	No	No	No	No	Yes	Yes
Socio-economic status	No	No	No	No	Yes	No	Yes	Yes
Prescriptions								
Unique product code	Yes (MINSAN)*	Yes (MINSAN)	Yes (MINSAN)	Yes (MINSAN)	Yes (HPK)	Yes (HPK)	Yes (PPA/BNF)	Yes (Varenummeret)
ATC code	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of Rx	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quantity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dosing regimen	Yes	No	No	No	Yes	Yes	Yes	Yes
Indication	Yes	Yes	No	No	Yes	No	No	Yes
In-patient use of drugs	No	No	No	No	No (free text if registered)	Yes (partly)	No	Yes (since 2006)
Prescription drugs	Yes (independent of reimbursement)	Yes (independent of reimbursement)	Yes	Yes	Yes (independent of reimbursement)	Yes (independent of reimbursement)	Yes	Yes (only reimbursed)
OTC drugs	No	No	No	No	Not validly	No	No	No

(cont.)

CHARACTERISTICS	**Pedianet** (Italy)	**Health Search** (Italy)	**Lombardy Regional SISR data** (Italy)	**Tuscany Regional SISR data** (Italy)	**IPCI** (Netherlands)	**PHARMO** (Netherlands)	**QRESEARCH** (UK)	**Aarhus University Hospital DB** (DK)
Outcomes								
Symptoms	Yes (free text)	Yes (free text)	No	No	Yes (free text/ICPC)	No	Yes	No
Out-patient diagnoses	Yes (ICD-9)	Yes	No	No	Yes (ICPC)	No	Yes	Yes
Hospitalisations	Yes (not complete)	Yes (not cause-specific)	Yes	Yes	Yes	Yes (ICD-9)	Yes	Yes
Out-patient specialist care	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Values of laboratory measurements	Yes	Yes	No	No	Yes	Yes	Yes	Yes (since 1997)
Potential confounding factors								
Smoking	-	Yes	No	No	Yes	No	Yes	Yes, in the Birth file
BMI	Yes	Yes	No	No	Yes	No	Yes	No

B 1.3 S/T Methodology and associated work plan

B 1.3.1 Overall strategy and general description

The work plan of the ALERT project has been carefully designed to cover all of the aspects that will require specific effort from the Consortium towards a successful completion. This includes, besides the core scientific and technological work packages, consideration of activities such as ethical surveillance, project quality and assessment, study of exploitation and self-sustainability strategies, and a strong validation scheme.

Validation Sets (WP2.2)

The project uses quantifiable outcome measures. The first action in this project is to define the "gold standards" that will be used to perform these measurements. This will entail the development of validation sets, which will be developed by partners who are currently heavily involved with spontaneous reporting systems and researchers who are experienced and actively involved in signal evaluation. One of the main results expected of this project is to provide a system for an *earlier* detection of ADRs. Moreover, the project claims also that this can be done without generating too many spurious signals. Based on recent literature and signals received by regulatory authorities, therefore, two validation sets will be developed: a set of true ADRs (that is, side effects recently established) and a set of spurious signals (that is, recent signals that caused concern but could not be proven in analytical studies).

The validation set of true ADRs will consist of drug-adverse reaction combinations that have previously been identified and established (e.g. tendon ruptures on fluoroquinolones, rhabdomyolysis on statins, myocardial infarction with COX-2 inhibitors). This validation set will be used throughout the project for testing the ability of the system to detect ADRs ("sensitivity").

The validation set of spurious signals consists of associations that were found by traditional pharmacovigilance monitoring but could not be proven in more analytical studies undertaken in response to the signal[43] (e.g. reserpine and breast cancer, increased risk of sudden cardiac death with sertindole). The rationale behind this validation set is our conviction that the benefit of a true-positive signal can only be interpreted in the light of its costs: the spurious signals. An explicit purpose of this project is therefore to unite the ability to find true signals with the ability to avoid false-positive signals. This validation set will be used to assess the ability of the system to improve on previous signal detection approaches ("specificity").

The validation sets will be developed *independently* from the electronic healthcare records. That is, data from the EHRs will *not* be used in the process of creating the validation sets. This is done to avoid methodological bias, by which, if EHRs were used to create these sets, the resulting system could be blamed for 'creating a self-fulfilling prophecy.'

According to scientific principles in pattern recognition, each validation set will be split in a learning set and a test set. Assignment to the learning or testing set will be at random. The learning sets will be made available early in the project and will be used throughout the development stages of the project (WP3, 4 and 5) to optimize the signal detection and analysis algorithms. The test sets will be set apart and will only be used in the advanced stages of the project to provide an unbiased estimate of the overall system performance.

[43] Hauben M, Reich L, Van Puijenbroek EP, Gerrits CM, Patadia VK. Data mining in pharmacovigilance: lessons from phantom ships. Eur J Clin Pharmacol 2006; 62: 967-70.

Event Sets and Terminology Mapping (WP2.1 and WP2.3)

All of the different databases in this project have their own specific coding schemes. Whereas one database may use ICPC, another may use READ coding or a version of ICD, and others might rely (in part) on free text. As a result, a mapping has to be developed that takes into account these local coding habits.

Fortunately, this mapping can be constrained: we are first and foremost interested in those events that, typically, are involved in adverse drug reactions. When reviewing literature, it is apparent that only a limited number of events are responsible for the majority of serious drug-related issues: e.g., hepatotoxicity, cardiac valvular disorders, arrhythmias, stroke, myocardial infarction, renal failure, ocular adverse effects, hypersensitivity, agranulocytosis, and immunological reactions, including anaphylactic shock. In order to constrain the task of terminology mapping, we will first define the *event set* (WP 2.1) on which the project will focus, on the basis of the current experience documented in scientific literature and obtained by evaluation of spontaneous reports combined with relevant coding schemes for side effects (e.g., MedDRA). During the course of the project, this event set might increase. The event set will constitute (enumerate) the specific clinical events that are being monitored. Subsequently, each participating database will specify the *mapping* of *local terminology* to this event set (WP 2.3). The mapping of local terminology into events is complicated by the fact that some databases rely on free text to record part of the data. Whereas free text is optimal to describe a specific situation, it is a limiting factor when the data has to be aggregated and/or mined. We foresee that for some databases a dedicated text mining effort will be required to translate the medical records to events of interest.

In *Figure 2*, the flow of data and information in the project is displayed. After definition of the events of interest, and mapping of those events to the participating databases (with the help of text mining for some databases), we will extract data and perform data mining to generate signals. These signals will be subsequently substantiated using biomedical knowledge, and thereafter validated to evaluate the system's capabilities.

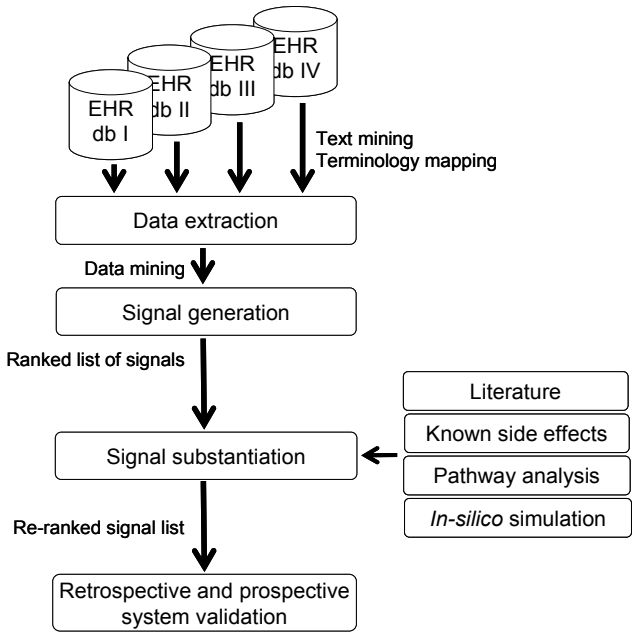


Figure 2: Based on shared terminology (e.g. the event set), signals are generated using the electronic healthcare records and subsequently substantiated using current biomedical knowledge. Retrospective and prospective validations constitute the final stages.

Signal Generation (WP3)

Data mining, epidemiological and computational techniques will be employed to detect signals from the EHR databases. This will be done by comparison of consecutively derived stratified (age, gender, co-morbidity) event rates by type of drug (looking in trends over time) and by comparison of event rates between drugs used for similar indications. In order to reduce spurious associations and signals, a temporal causality framework will be used. This consists of using the correct temporal relationship between time of drug administration and adverse reactions, strength of an association, dose response, and reduction of confounding factors (i.e. other factors that may cause the outcome). Data on age, sex, indication and covariates extracted from the EHR will be used to reduce confounding factors. Stratification for age and gender will allow for initial identification of subpopulations at higher risk of ADRs.

Model fitting and prediction will be based on conventional statistical modelling techniques such as logistic regression, and will be complemented by machine learning methods for supervised classification, which allow for non-linear relationships and can control overfitting where there are more variables than observations. In addition, techniques developed in pharmacoepidemiology will be used (e.g. monitoring specific cohorts of (new) users in combination with controls).

Throughout the project, emphasis will be placed on avoiding, as much as possible, the generation of spurious signals. Already in the signal generation stage, methods to reduce spurious signals will be employed. Methodological approaches that reduce the likelihood of chance findings will be the preferred methods. During data mining in the EHRs, for example, this means that we will use independent learning and test populations, to allow for independent evaluation of the generated signals. Data mining will be conducted on the learning populations; subsequent verification will be done on the test populations. Separation in learning and test populations will be done in two ways: by splitting each EHR database in a learning and test set, and by using one of the EHR databases (e.g. IPCI) for learning, and another (e.g. QRESEARCH) for testing.

The data mining in the EHRs will result in a prioritized list of signals, based on the strength of the association.

Signal Substantiation (WP4)

The generation of false-positive signals constitutes a major concern in pharmacovigilance. False-positive signals constitute a public health hazard. An overabundance of false-positive signals overwhelms regulatory agencies and diverts limited resources. False alarms may trigger unwarranted warnings or even withdrawal of drugs. Data mining of spontaneous reporting systems has been shown to generate considerable amounts of false-positive signals, and this is still expected to be the case if signals are generated on the basis of EHR data alone. Therefore, various additional sources of information will be used in ALERT to reduce the number of spurious signals. These information sources will be used to find evidence that supports or discounts the signals produced in the data mining stage.

The list of potential signals will be assessed by automatically investigating feasible paths connecting the drug and the adverse reaction involved in the proposed signal. For such a purpose different computational techniques will be used. The general strategy is the automatic linkage of biomedical entities (drugs, proteins and their genetic variants, biological pathways and clinical events) by means of data mining approaches and *in silico* predictions based on biomolecular structures. The biological annotations of the considered drug will be expanded by automatically detecting its metabolites and other molecules showing similar pharmacophoric patterns. Data and text mining techniques will be used on pharmacological repositories (e.g., Meyler's Side Effects of Drugs, Martindale, DRUGDEX, Summary of Product Characteristics, etc.) and biomedical literature (Medline) in order to detect associations between the aforementioned biomedical entities. *In silico* simulations of drug-target interactions will also be performed. Proteins interacting with the drug or related molecules will be mapped into biological pathways that could be involved in the

clinical event which is part of the signal. The existence of inherited (autosomal) genetic polymorphisms that can affect drug pharmacokinetics, as well as the biological behavior of targets and anti-targets (i.e. drug pharmacodynamics), collectively known as pharmacogenetics, will also be considered. Moreover, frequencies of phenotypically relevant polymorphisms in genes coding for drug metabolizing enzymes and drug targets may differ between ethnic groups. Effects of such polymorphic alleles on pharmacovigilance could potentially be captured by the proposed project as differences between ethnic groups in ADR rates and drug efficacy.

Using these various techniques, the signal substantiation stage will aim at answering, for each signal, the question: "Does current biomedical evidence support this signal?"

This process should be largely automated, not only in view of the number of signals to be checked, but also to accommodate the rapid expansion of information in the biomolecular field. For example, changes in the information sources (e.g. our understanding of certain pathways) may also have an impact on the assessment of a signal, and should be dynamically accounted for in the signal substantiation stage. As changes of the information sources occur frequently, the process of re-evaluating the signals must be automatic in order to be tractable.

System integration (WP5)

We view system integration from *two perspectives*. The first perspective deals with *combining evidence* from diverse components of the generation and assessment of the signal to produce a "final outcome". The second perspective is on a more technical level: the developed signal detection algorithms and the data sources described above (WP3 and WP4) will be integrated in a computerized ADR detection and monitoring *system*. That system should allow users to quickly inspect the underlying EHR data, relevant literature, and pertinent information from any data source that was used to generate and assess the signals.

In this proposal, it is argued that electronic healthcare records can be used to generate signals and that subsequent analysis of those signals in the light of our current understanding of biomedical processes allows us to assess these signals. That is, if for a given signal no biomedical supporting evidence can be found at a mechanistic level (e.g. by the analysis of currently known molecular pathways), the signal is more likely to be spurious; as a result, the signal should be re-ranked in a prioritized list. This however involves the development of an evidence weighting scheme to combine the various pieces of information and present the user with a final list of ranked signals (WP 5.1). Some research on how to combine different evidence has already been published. Little of that research, however, has to do with the assessment of signals for side effects of drugs based on electronic healthcare records. As a result, little or no literature is available that documents evaluation of weighting/combining schemes in the context of EHR-generated potential ADRs. The availability of both signals generated in electronic healthcare records and a validation set of "true" and spurious signals will provide us with an opportunity to study the behaviour of various schemes to combine evidence (e.g., Bayesian belief nets, fuzzy logic, and predicate logic).

In combining the evidence, the trade-off between "true" ADRs and spurious signals will become very explicit. The variety of possible methods to combine evidence will result in a receiver-operator characteristics curve that brings home the message that each cut-off point is characterized by both false positives and false negatives. The desire to make this trade-off an explicit topic of evaluation is one of the reasons this project uses *two* validation sets (true ADRs and spurious signals).

Integration on the level of a *system* requires a technical effort to put all the diverse components that constitute both the generation and assessment of a signal in a uniform, web-based environment (WP 5.2). The information used by the system should be easily accessible to facilitate the signal evaluation process.

Integration on the level of a system will also include the ability to re-evaluate a signal. That is, the system should allow for regular monitoring of signal strengths over time. The content of electronic healthcare records will change over time (e.g. more people taking a drug will increase the "power" of that data set, more EHR databases could be 'enlisted' into the federated ALERT scheme, etc.), but also our understanding of biological mechanisms will evolve (e.g. new or different molecular pathways will become available). In the light of these changes, re-evaluation may be mandated. As a consequence, the final system needs not only to keep track of the dates when a given analysis was performed, but also should facilitate the re-execution of (parts of) the analysis.

System validation (WP6)

As shown in *Figure 3*, validation during system development will be done iteratively using the validation learning sets. Initially, a limited set of adverse events will be used to develop and refine the detection and substantiation algorithms. This set will gradually be expanded to cover a range of important type A and B adverse events, notably hepatotoxicity, cardiac valvular disorders, arrhythmias, stroke, myocardial infarction, renal failure, ocular adverse effects, agranulocytosis, hypersensitivity immunological reactions, including anaphylactic shock.

The system will then be tested retrospectively using the validation test sets (WP 6.1). The system's ability to rediscover drug-event combinations from the test set with known side effects will provide an indication of the sensitivity of the system. The system's ability not to signal drug-event combinations from the test set with spurious signals, and its capability not to identify indications of the drug as signal, will provide an indication of the specificity of the system.

In addition to retrospective validation, a prospective evaluation will be done by further investigating the top-ranking signals generated by the system (WP 6.2). For the verification of these top-ranking signals, traditional hypothesis testing approaches, including analytical pharmaco-epidemiological studies, will be followed. For evaluation purposes, only EHR data that has not previously been involved in the development of the signal detection algorithms will be used.

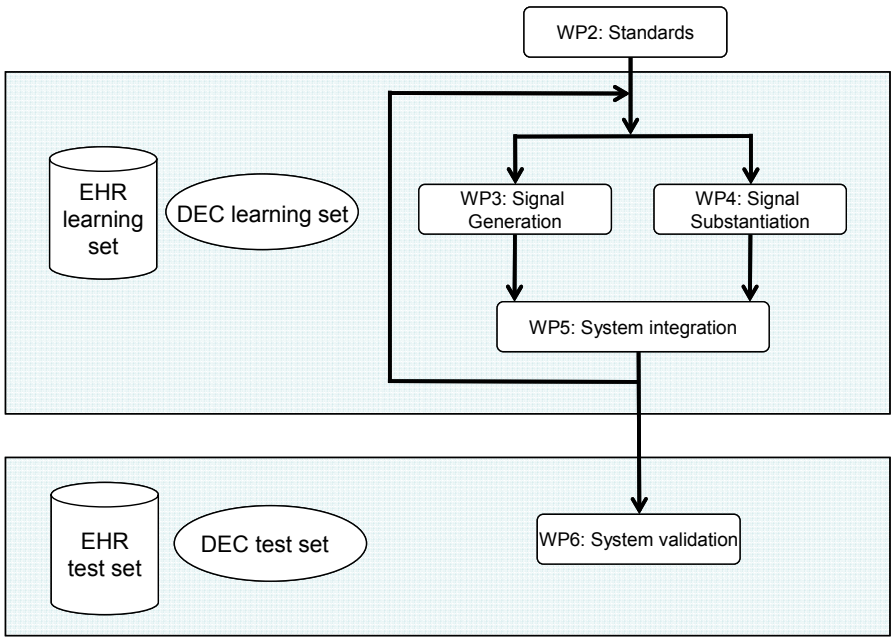


Figure 3: Validation of the system will be performed in all stages of the project. In the development stages of the project, validation will be done with learning sets of adverse events and spurious signals. In later stages of the project, a retrospective validation with independent test sets will be performed. Prospective validation will be undertaken as well.

The results of the newly developed system will be compared with those of spontaneous reporting systems to assess the system's capability of faster and more precise discovery of ADRs. For this evaluation, we will compare recently established ADRs (e.g. rofecoxib and myocardial infarction) in the literature with automated analysis of the EHRs prior to the date of the first reports of that side effect in the literature.

Dissemination and exploitation (WP7)

As a key component in the work plan, dissemination activities will be undertaken according to a well-defined communication plan. This will detail the objectives, target audiences, activities and tools to be used for communication purposes. This activity will have a strategic importance not only to disseminate information about the project and its achievements, but also to engage other actors and initiatives in the field, so as to ensure wide usage and impact of the ALERT system.

In connection with these aspects, the issue of exploitation of the project's results will be also carefully considered. On the one hand, background owned by participants will have to be respected in any future exploitation scenario. On the other hand, the system should explore and define ways to ensure sustainability in the long term (i.e. after the EC funding period). The primary target users of ALERT are regulatory authorities, researchers in the area of drug safety, pharmaceutical companies and EHR database owners. All of these stakeholders will have to be actively enlisted, and the project should be able to raise their interest during its duration. Discussions on suitable exploitation models should then naturally follow, and be reinforced by encouraging results from the validation exercises. Potential scenarios will be discussed taking into account the normal working flow of the ALERT "engine", which depends on a number of EHR databases to become interested in the initiative and be actively linked to the federation scheme proposed.

Both dissemination and exploitation activities will be undertaken in the framework of WP7.

Scientific Coordination and Project Management (WP1 and WP8)

Last, but not least, appropriate coordination and management activities are also a key component to round up the work plan. Scientific Coordination will deal with strategic direction and supervision of scientific and technical work. It will also comprise the definition of quality policies and continuing assessment of the project's degree of success. Finally, it will entail ethical supervision to ensure that all the relevant regulations are fully complied with, especially in relation with the use of EHR data. Management will put all the contractual, administrative and financial mechanisms in place so as to ensure a smooth working flow during the project lifetime. In the framework of a dual leadership structure, it will support the Scientific Coordination in daily management of the work plan, ensuring that trade-offs between key variables (scope, quality, time, cost) are optimally solved.

Risk analysis

Risks are inherent to any research project. Although the work plan includes risk management as a continuous activity within WP8, and the Consortium has been carefully selected to include outstanding expertise and productivity, some risks do already exist in relation with the proposed work. The three main risks detected at the current stage are listed hereunder, with estimation of their probability ("P", ranging from 1-Low to 3-High), and potential impact ("I", ranging from 1-Low to 3-High). An index ("r") for each risk is constructed multiplying probability by impact, so as to allow for prioritization.

Excessive detection of false signals by the ALERT system (P=1; I=3; r=3). The impact of a false signal should not be underestimated: a false signal can have grave consequences both for the population at large (e.g. by inhibiting the use of an effective drug) and the company that produces

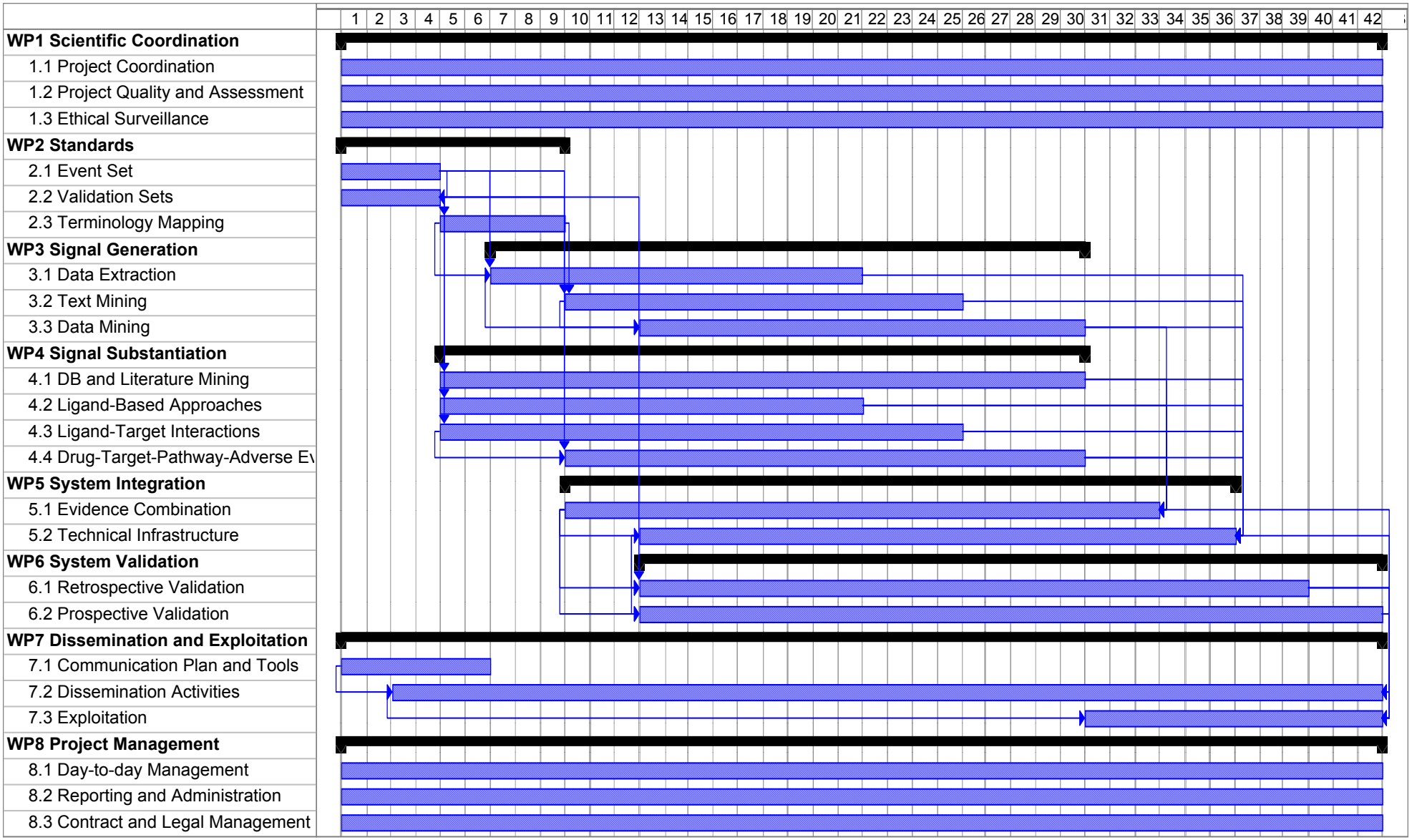
the drug (e.g. a once damaged reputation of a drug is difficult to reclaim). One of the most important outcomes of the project will, therefore, be the ability to avoid spurious signals. Hence, I=3, as the recognition of recent "false" signals is one of the major quantifiable outcomes of this project. It should be noted that the system is not meant to replace but to supplement the clinical judgment of safety reviewers.[44] However, there is a risk that the final system is not specific enough to rule out false signals to a large enough extent. Mitigation actions already embedded in the work plan include the consideration of quality assurance activities and, most notably, strong validation exercises (both retrospectively and prospectively) within an iterative development model, which should guide system refinement until performance is consistently good. The existence of independent validation sets will help empower these validation activities, hence P=1. If, however, these measures are not enough and it is detected halfway through the project that system performance is under par, contingency plans include the generation of additional development-validation iterations (shorter cycles focused on problematic issues), and the re-arrangement of efforts and resources towards supplementing these activities.

Failure to raise the interest of key stakeholders (P=1; I=3; r=3). The Consortium has strong links with regulatory authorities at the national levels – some of them have already agreed to be part of the Scientific Advisory Board, hence P=1. However, the ambition of ALERT is to become a widely used tool that can really make a significant impact on the detection of ADRs, and the initiative only makes sense if it manages to attract users and other stakeholders that can ensure its sustainability over time, hence I=3. Mitigation for this risk entails appropriate consideration of active dissemination and exploitation tasks in the work plan, and the continuous use of the existing contacts to generate awareness and 'enlistment'. Should this be perceived as insufficient, contingency plans would include the reinforcement of links with other European and international initiatives (including other EU projects in the area), and the assignment of additional resources to the dissemination and exploitation tasks.

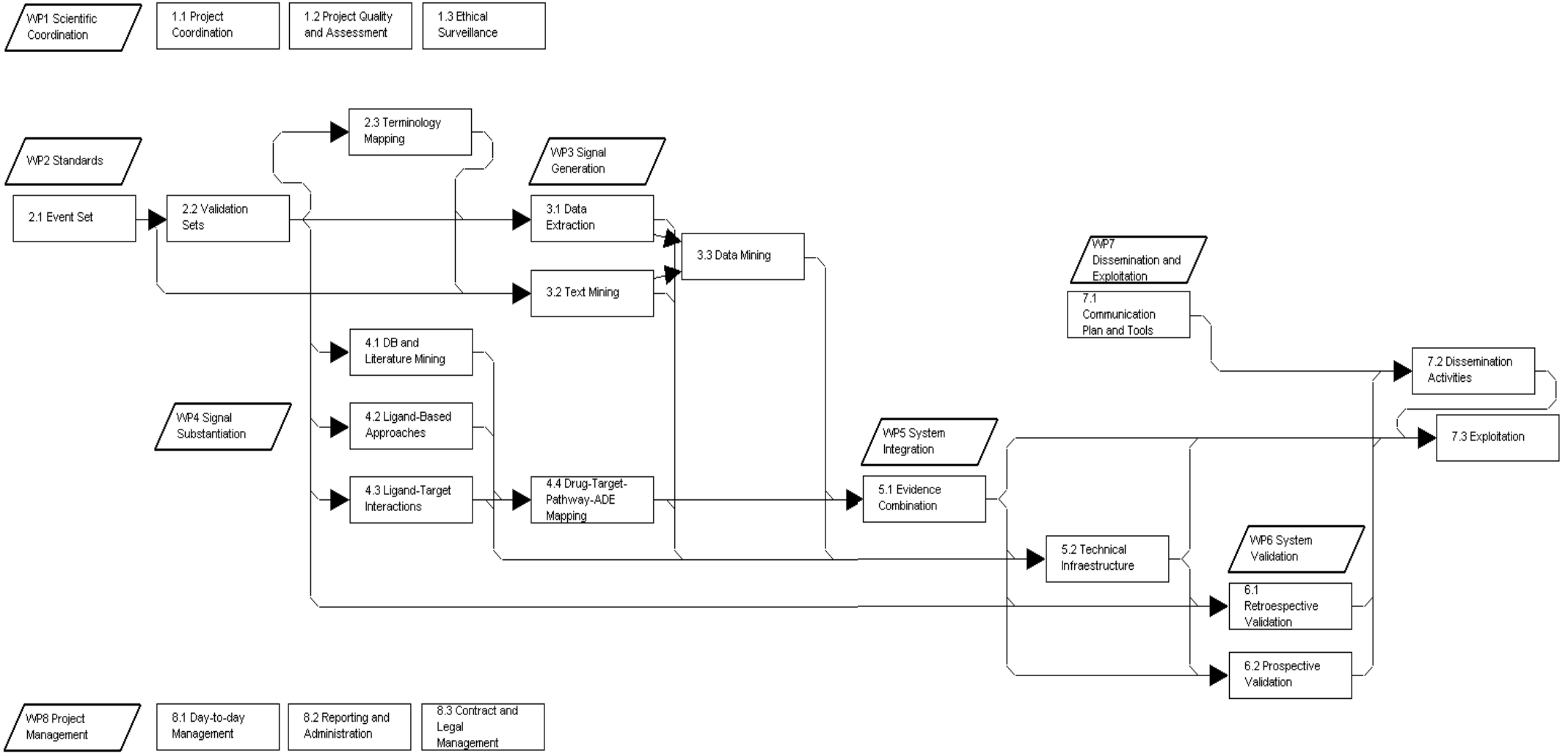
Failure to engage other EHR databases into the proposed federated scheme. (P=2; I=1; r=2). ALERT is designed as an open framework that should allow for incorporation of additional EHR databases in a federated scheme, which would enrich the system and make it more powerful to early detect ADRs. Therefore, there is a need to raise interest among other European EHR databases. However, there is a risk that due to ethical or legal restrictions, difficulties with different languages and/or data structures, lack of resources, or simply because the initiative is not attractive enough, no more databases can be engaged. Because of the variety of potential reasons for lack of engagement, P=2. However, the project already includes data sources comprising information of 30 million individuals, so the project objectives would not be hampered if no new clinical databases are enlisted during the project life, hence I=1. Mitigating this risk, active dissemination activities will include EHR owners/producers as one of the main target groups, and exploitation studies will duly consider these aspects as part of the sustainability scenarios. Partners having links with other EHR databases will also be encouraged to promote their enlistment, and resources for inviting external actors to meetings, etc. are already budgeted for. Contingency plans include more active outreach to specific, important EHR databases, reinforcing the visibility of the validation results and of the potential benefits of being involved in the federated scheme, and specific efforts to ease the incorporation of them into the ALERT structure, including the use of small parts of the funding for potential inclusion of the responsible organizations as active participants in the project to reinforce their incentives.

[44] Trontell A. Expecting the unexpected--drug safety, pharmacovigilance, and the prepared mind. N Engl J Med 2004; 351:1385-7.

B 1.3.2 Timing of work packages and their components



Graphical presentation of work packages (PERT diagram)



B 1.3.3 Work package list / overview

Work package list

Work package No	Work package title	Type of activity	Lead beneficiary no.	Person-months	Start month	End month
1	Scientific Coordination	RTD	1	40.1	1	42
2	Standards	RTD	6	40.4	1	9
3	Signal Generation	RTD	1	239.6	7	30
4	Signal Substantiation	RTD	3	160.1	5	30
5	System Integration	RTD	4	120.0	10	36
6	System Validation	RTD	5	104.2	13	42
7	Dissemination & Exploitation	OTHER	2	39.8	1	42
8	Project Management	MGT	2	56.2	1	42
	TOTAL			**800.4**		

B 1.3.4 Deliverables list

List of Deliverables – to be submitted for review to EC[45]

Del. no.[46]	Deliverable name	WP no.	Lead beneficiary	*Estimated indicative person-months*	Nature[47]	Dissemination level[48]	Delivery date[49] (proj. Month)
1.1	Report on Ethical Issues Relevant for the Project	1	1	4.1	R	PU	3
8.1	Project Handbook	8	2	3.0	R	CO	3 (*)
2.1	List of Events to be Monitored	2	6	12.0	R	PU	4 (*)
2.2	Two Validation Sets with Supplementary Information	2	6	8.0	R	PU	4
1.2	Quality Assurance Guidelines and Procedures	1	1	8.0	R	CO	6 (*)
7.1	Communication Plan	7	2	4.0	R	CO	6
2.3	Medical Event and Drug Terminology Standardisation and Mapping Scheme	2	6	20.4	R	PU	9
7.2	Report on the ALERT Communication Tools	7	2	4.0	R	PU	12 (*)
8.2	Technical and Financial Annual Reports #1	8	2	17.0	R	CO	12
4.1	Report on the Mining of Pharmacological Databases and Repositories	4	3	25.0	R	PU	15
1.3	Interim Assessment of the Project	1	1	20.0	R	CO	21 (*)
3.1	Description of the Common Data Framework and Software for Local Data Extraction	3	1	144.0	R,P	PU	21

45 In a project which uses 'Classified information[45]' as background or which produces this as foreground the template for the deliverables list in Annex 7 has to be used

46 Deliverable numbers in order of delivery dates: D1 – Dn

47 Please indicate the nature of the deliverable using one of the following codes:
R = Report, **P** = Prototype, **D** = Demonstrator, **O** = Other

48 Please indicate the dissemination level using one of the following codes:
PU = Public
PP = Restricted to other programme participants (including the Commission Services)
RE = Restricted to a group specified by the consortium (including the Commission Services)
CO = Confidential, only for members of the consortium (including the Commission Services)

49 Month in which the deliverables will be available. Month 1 marking the start date of the project, and all delivery dates being relative to this start date. Deliverables marked with "(*)" will be sent to the Commission only upon request.

Del. no. [46]	Deliverable name	WP no.	Lead beneficiary	*Estimated indicative person-months*	Nature[47]	Dissemination level [48]	Delivery date[49] (proj. Month)
4.2	Description of Ligand-Based Approaches	4	3	34.3	R,P	PU	21
5.1	Interim Report on Evidence Combination	5	4	36.0	R	PU	21 (*)
7.3	Intermediate Report on Dissemination Activities	7	2	13.0	R	PU	24 (*)
8.3	Technical and Financial Annual Reports #2	8	2	17.0	R	CO	24
5.2	ALERT System Software Version 1	5	4	24.0	P	CO	24
3.2	Description of the Text Mining Algorithms and Text Mining Software	3	1	24.0	R,P	CO	25
4.3	Report on Ligand-Target Simulations	4	3	32.0	R	CO	25
6.1	Interim Report on Retrospective Validation	6	5	28.6	R	RE	27
3.3	Description of the Data Mining Algorithms and Data Mining Software for Local Signal Generation	3	1	71.6	R,P	CO	30
4.4	Report on Literature and DB Mining	4	3	32.0	R,P	RE	30
4.5	Report on Drug-Target-Pathway-Adverse Event Mapping	4	3	36.8	R,P	CO	30
6.2	Interim Report on Prospective Validation	6	5	31.2	R	CO	30
5.3	Final Report on Evidence Combination	5	4	36.0	R	PU	33
5.4	Final Version of the ALERT System Software	5	4	24.0	P	CO	36
6.3	Final Report on Retrospective Validation	6	5	23.4	R	PU	39
1.4	Final Report on Ethical Issues	1	1	8.0	R	PU	42
6.4	Final Report on Prospective Validation	6	5	21.0	R	PU	42
7.4	Final Report on Dissemination Activities	7	2	12.8	R	PU	42

Del. no. [46]	Deliverable name	WP no.	Lead beneficiary	*Estimated indicative person-months*	Nature[47]	Dissemination level [48]	Delivery date[49] (proj. Month)
7.5	Report on Exploitation and Sustainability Plans	7	2	6.0	R	CO	42
8.4	Technical and Financial Annual Reports #3	8	2	19.2	R	CO	42
	TOTAL			**800.4**			

B 1.3.5 Work package descriptions

Work package description

Work package number	1			**Start date or starting event:**			1					
Work package title	Scientific Coordination											
Activity type	RTD											
Participant number	**1**	2	3	4	5	6	8	10	11	12	13	14
Participant short name	**EMC**	FIMIM	UPF	UAVR	NEUROLESI	UB2	AUH-AS	UNOTT	UNIMIB	ARS	PHARMO	PEDIANET
Person-months per beneficiary	**14.1**	6.3	2.3	2.3	3.8[a]	2.3	1.5	1.5	1.5	1.5	1.5	1.5

Objectives

(a) To provide the overall scientific direction and to drive the progress of the project, steering efforts of the partners for the achievement of milestones and ensuring that the work is undertaken with appropriate quality levels.

(b) To provide a unified scientific and technological view and strategy that reinforces the integration of the different resources and tasks towards the unique system that the project aims to develop and validate.

(c) To continuously assess the degree of fulfilment of the project's objectives.

(d) To ensure that the project is not hampered by ethical problems and respects all relevant international and national regulations in this regard.

Description of work

This work package includes three main tasks.

1.1 Project Coordination

This task will involve general project leadership and coordination at the scientific and technical levels. By the application of good scientific knowledge and relationships, the strategic direction of all scientific and technical activities will be monitored and steered optimally. This will involve using not only skills and expertise available within the Consortium, but also promoting the contacts and relationships with other initiatives in the area concerned. Given the significant number of partners and disciplines involved in this project, scientific coordination will to a large degree concentrate on providing cohesion and focus with a view on ultimate success. This will entail awareness on scientific progress in the field and any key emerging issues, working with the Work Package Leaders (in particular) to refine and refocus project activities as necessary.

Close coordination with management activities in WP8 is a must for this WP, as the tandem between the Scientific Coordinator and Project Manager is envisaged as the main 'driving force' that helps to propel efforts towards successful completion (see section 2.1 of this proposal). The robust management structure designed for the project will be instrumental in accomplishing this project leadership. Leadership decision will also be substantially influenced by reference to advice

[a] Of which 1.5 person-months correspond to subcontractor SIMG.

garnered by coordinating the project Steering Committee, Scientific Advisory Board and other ad-hoc Committees that may be set up as needed. To closely monitor project progress, frequent communications will take place (e.g. at least monthly) between the coordinator and the work package leaders, and this will help to re-enforce (with efforts of WP8) the timely gathering of contributions, the achieving of milestones, and the delivery of deliverables.

This activity will be led by EMC, with contribution from work packages leaders (FIMIM, UPF, UAVR, NEUROLESI, UB2).

1.2 Project Quality and Assessment

High quality standards will be applied to all the work undertaken. Good performance will be a priority of the project, and this will be fostered by openness about achievements, friendly peer-pressure, and constructive criticism. Special relevance will be given to this activity in General Consortium meetings, in order to acknowledge all partners about the quality procedures. This will be strengthen on the technical level by enforcing the use of formal procedures for testing and validating all software developed in the project, and by developing early in the project quality guidelines that affect all work and procedures that need to be implemented.

This activity will also entail the continuing assessment of the project as regards to degree of fulfilment of its objectives and validation of its scope. This activity will span throughout the project but will be especially enforced as a result of the validation activities to be carried out in WP6, insofar as they will provide objective measurement of the intended benefits of the system. Additionally, the assessment activity will evaluate the strengths and weaknesses of the project as they evolve during its duration. In that sense, they will also be related with the risk management tasks to be undertaken under WP8.

This activity will be led by EMC with contribution from FIMIM.

1.3 Ethical Surveillance

This activity will provide ethical oversight, analysis, and guidance on all aspects of the ALERT project. As a starting point for the guidance, Consortium members aware of the EHRs regulations dealing with ethical use of the data and adequate privacy control, informed consent, etc. will be asked to report their assessment of ethical issues affecting (or likely to affect) the project. A study about how the EHR databases involved in the project have implemented their ethical framework will be carried out during the first three months, encompassing a description of the existing rules, including data protection issues, in use in each of the involved countries, with specific attention to databases containing children information. This will help to ensure that during the project life all relevant regulations are fully complied with. Regular updates of this information will be promoted so that ethics are continuously being considered throughout the project. If and as needed, ethics experts will be engaged through the Scientific Advisory Board or a specific ad-hoc Committee.

All participants involved in one or more of the EHR databases in the project (EMC, NEUROLESI, AUH-AS, UNOTT, UNIMIB, ARS, PHARMO, PEDIANET, together with subcontractors as appropriate) will contribute to this task.

Deliverables

D1.1: Report on Ethical Issues Relevant for the Project. (month 3)

This deliverable will offer a 'roadmap' concerning the state of the art of the methodology used regarding ethical issues in the participating databases, as well as the rules they follow and the procedures in place according to national regulations. The Report will clarify processes and

procedures relevant to informed consent, how it is obtained in the relevant circumstances and justify when it was not considered necessary. It will summarise the experience of database owners in the Consortium regarding implementation of ethical principles and regulations, an assessment of ethical issues that may affect the ALERT project, and plans for dealing with them.

D1.2: Quality Assurance Guidelines and Procedures. (month 6)

A set of quality assurance principles to be applied in all work to be developed during the project, especially regarding the development and testing of the different pieces of software to be produced.

D1.3: Interim Assessment of the Project. (month 21)

Halfway through the project, an assessment of the degree of fulfilment of the objectives of the project will be carried out and reported in this deliverable.

D1.4: Final Report on Ethical Issues. (month 42)

A summary of ethical issues encountered during the project and how these have been solved.

Work package number	2		**Start date or starting event:**		1					
Work package title	Standards									
Activity type	RTD									
Participant number	1	3	5	**6**	7	8	10	11	12	13	14
Participant short name	EMC	UPF	NEUROLESI	**UB2**	LSHTM	AUH-AS	UNOTT	UNIMIB	ARS	PHARMO	PEDIANET
Person-months per beneficiary	1.7	1.7[a]	11.7[b]	**11.7**	3.4[c]	1.7	1.7	1.7	1.7	1.7	1.7

Objectives

(a) To define a list of important adverse events that should be monitored.

(b) To compile two validation sets of signals (drug-event combinations), to be used throughout the project for learning and testing purposes.

(c) To provide a mapping between the different terminologies used in the EHR systems.

Description of work

This work package includes three tasks that are related to the three objectives mentioned above.

2.1 Event Set

The first task involves the definition of a range of events that are considered to be important adverse drug reactions. For all of these selected events, definitions should be provided as well as a list of drugs and conditions that are known to be associated with these events, and could act as potential confounders. The list of adverse events resulting from this task will provide focus for the rest of activities in this WP.

Participant UB2 will lead this task, in close cooperation with NEUROLESI.

2.2 Validation Set

The second task involves the definition of two sets of signals (drug-event combinations), one set consisting of signals that in the past were found to be true positive (e.g. rofecoxib and myocardial infarction), the other set consisting of signals that were found to be spurious (false positives, e.g. reserpine and breast cancer). Selected signals will first be limited to those that include adverse events from the event list defined in task 2.1. The sets will be compiled based on data from the literature, health safety agencies, and pharmacovigilance centres, including data on drug withdrawals. The sets should contain a mixture of type A and type B adverse drug reactions, and include the year (and possibly month) of first occurrence of the signal, together with and a short description of the evidence that was used to support or discount the signal. Each validation set should consist of drug-event combinations of which half will be used during system development, and half will be used for retrospective performance validation of the final adverse event detection system resulting from WP5.

Participants UB2 and NEUROLESI, which have ample experience in signal detection and validation, will be involved in this task.

[a] Of which 1.7 person-months correspond to subcontractor TAU.
[b] Of which 1.7 person-months correspond to subcontractor SIMG.
[c] Of which 1.7 person-months correspond to subcontractor ICL.

2.3 Terminology Mapping

The third task involves the choice of a common, standard terminology for adverse events and for drugs, and the definition of a mapping scheme between the specific terminologies used in the different databases, in relation with the standard terminology chosen. The different EHR databases in the project use various systems for the coding of clinical symptoms and events (e.g. ICD-9-CM, ICPC, READ) and of drugs (ATC, BNF/PPA). Moreover, in some databases part of this information is only available in free text. An important consideration is that the mapping of free text to adverse event codes should allow for different languages. The meta-thesaurus of the Unified Medical Language System (UMLS) provides links between different terminologies and shall be used as a starting point for this specific issue.

All participants that are involved in one or more of the EHR databases in the project (EMC, UPF, NEUROLESI, UB2, LSHTM, AUH-AS, UNOTT, UNIMIB, ARS, PHARMO, PEDIANET, together with subcontractors as appropriate) will contribute to this task, sharing their know-how and making available the terminology used within their system.

Deliverables

D2.1 List of Events to be Monitored. (month 4)

This deliverable will comprise a list of important adverse drug reactions (and associated potential confounding factors) on which the rest of activities will focus.

D2.2 Two Validation Sets with Supplementary Information. (month 4)

Detailed description of two validation sets of signals to be used for system development and validation.

D2.3 Medical Event and Drug Terminology Standardisation and Mapping Scheme. (month 9)

This deliverable will map terminologies of events and drugs across the EHR databases in the Consortium, including consideration of language issues in databases that use free text.

Work package number	3		**Start date or starting event:**		7				
Work package title	Signal Generation								
Activity type	RTD								
Participant number	**1**	5	7	8	10	11	12	13	14
Participant short name	**EMC**	NEUROLESI	LSHTM	AUH-AS	UNOTT	UNIMIB	ARS	PHARMO	PEDIANET
Person-months per beneficiary	**54.7**	27.3[a]	13.0[b]	22.5	22.5	22.5	22.5	27.3	27.3

Objectives

(a) To establish a common data framework that allows to extract the relevant data from each EHR system for subsequent text and data mining processing.

(b) To develop text mining techniques that detect the selected medical events in free-text and map these terms to corresponding standard codes.

(c) To develop data mining algorithms that produce a prioritized set of adverse drug reaction signals.

Description of work

This work package consists of three tasks, corresponding with the three objectives above.

3.1 Data Extraction

A common data framework needed for further data extraction from the EHR databases will be established. An information model will be defined, delineating the data elements to be extracted (pre-specified medical events from WP2, drugs, time stamps, prescription data, age, sex, other covariates). For each EHR system, dedicated data extraction software (database queries) will be developed. This software will take into account the terminology mapping and the medical event list defined in WP2. The software should produce a data matrix that can be used as an input for data mining algorithms.

All data providers (EMC, NEUROLESI, AUH-AS, UNOTT, UNIMIB, ARS, PHARMO, PEDIANET, together with subcontractors as appropriate) will be involved in the definition of the information model. Each provider will be responsible for the development of the extraction software for its own database. This task will be globally led by EMC.

3.2 Text Mining

For those EHR systems that contain free text (IPCI, PHARMO, PEDIANET, HS), text mining algorithms will be developed to find the pre-specified medical events (as defined in the event list resulting from WP2) in the text and map them to the appropriate codes. The algorithms should be able to cope with different languages. For each system, a manually annotated set of EHRs (both positive and negative examples of events) will be compiled to be used for learning and testing purposes.

This task will be led by EMC with contribution from PHARMO, PEDIANET and NEUROLESI's subcontractor. Algorithm development will be done by EMC.

[a] Of which 27.3 person-months correspond to subcontractor SIMG.
[b] Of which 6.5 person-months correspond to subcontractor ICL.

3.3 Data Mining

Data mining techniques will be employed to detect ADR signals from the EHR databases. Firstly, conventional statistical and epidemiological techniques will be used by comparison of consecutively derived, stratified (age, gender, indication) event rates by type of drug (looking in trends over time) and by comparison of event rates between similar drugs. In order to reduce spurious associations and signals, a causality framework will be used. This consists of using the correct temporal relationship between time of drug administration and event, strength of an association, dose response, and reduction of confounding factors (i.e. other factors that may cause the outcome). Data on age, sex, indication and covariates extracted from the EHR will be used to reduce confounding factors. Special attention will be given to the detection of ADR signals in children and other at risk groups such as elderly people and patients with certain co-morbidities. The data mining in the EHRs will result in a prioritized list of ADR signals, based on the strength of the association in comparison with the oldest drug in the therapeutic and chemical class. In addition to the conventional statistical and epidemiological techniques, machine learning methods for supervised and unsupervised classification techniques will explored, not only to detect single drug-single adverse event combinations, but also multiple drugs-single AE (drug-drug interaction) and single drug-multiple AEs (syndromes).

This activity will be led by EMC. Participants LSHTM, AUH-AS, UNOTT, UNIMIB, ARS, PHARMO, PEDIANET and NEUROLESI, will be also working in this activity.

Deliverables

D3.1 Description of the Common Data Framework and Software for Local Data Extraction. (month 21)

The final data framework and software resulting from the data extraction activity will be comprehensively described in this deliverable.

D3.2 Description of the Text Mining Algorithms and Text Mining Software. (month 25)

The algorithms and software developed to mine EHR databases that comprise free text will be comprehensively described in this deliverable.

D3.3 Description of the Data Mining Algorithms and Data Mining Software for Local Signal Generation. (month 30)

This deliverable will describe the complete set of methods, algorithms and software developed for data mining of the EHR databases resulting in generation of a primary signal list.

Work package number	4	**Start date or starting event:**		5		
Work package title	Signal Substantiation					
Activity type	RTD					
Participant number	1	**3**	5	6	7	9	15
Participant short name	EMC	**UPF**	NEUROLESI	UB2	LSHTM	AZ	USC
Person-months per beneficiary	14.8	**64.1**[a]	7.4	7.4	7.4	41.9	17.1

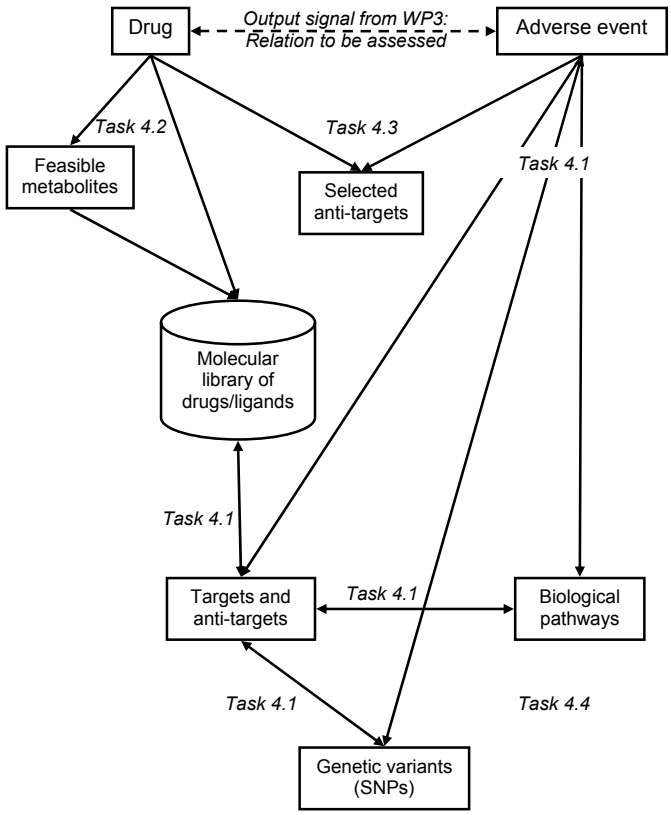
Objectives

To automatically detect scientifically and mechanistically sound explanations for the signals obtained in WP3 by means of a combination of analyses of repositories of known side effects, biomedical literature, *in silico* predictions and pathway mapping.

Description of work

Most of the drug adverse events are mechanistically related with off-target affinities, drug metabolism phenomena and inter-individual genetic variants, most notably single nucleotide polymorphisms (SNPs). The general strategy of this work package is the automatic linkage of biomedical entities (drugs, proteins and their genetic variants, biological pathways and clinical events) by means of data mining approaches and *in silico* predictions based on biomolecular structures. In this way, signals generated in WP3 will be assessed according to the degree to which current biomedical knowledge allows for their substantiation. The relationships to be substantiated, detailed in the figure below, will be addressed in four main tasks.

[a] Of which 7.4 person-months correspond to subcontractor TAU.



4.1 DB and Literature Mining

Computational algorithms will be designed and implemented with the aim of detecting scientifically substantiated relationships between pairs of entities that combine the following categories: (a) drugs, (b) proteins and their genetic variants, (c) biological pathways, and (d) adverse events. In order to find previously established relationships between drugs and adverse events, we will develop software that processes information in specialized databases and electronic repositories such as Meyler's Side Effects of Drugs, Martindale, DRUGDEX, SPCs, Physician Desk Reference, etc. Text mining strategies will be designed and implemented to automatically detect feasible pair-wise relationships between entities of the aforementioned categories. In addition to mining specialized databases, text mining will also be performed on the 16 million abstracts stored in the Medline database and, whenever available, the full text of the corresponding articles. In mining literature, a thesaurus-based approach that allows concept recognition and identification will be followed. The goal of this text mining will not only be to retrieve articles in which concepts co-occur (possibly within a certain text window, or within the same sentence), but also to retrieve "indirect co-occurrences". The latter approach builds on previously developed technology, in which a concept is characterized by a "concept profile", a list of contextual terms derived from the literature. Concept profiles can be matched using a score, which expresses the strength of relationship between the corresponding concepts. In addition, algorithms that take into account the chemical nomenclature of drugs will be developed and applied to extract chemical information from literature.

This task will be led by EMC with a major contribution from UPF. NEUROLESI, UB2 and LSHTM will also contribute.

4.2 Ligand-Based Approaches

A way of detecting veiled drug-adverse event relationships is the computational analysis of the similarities between the pharmacophoric patterns of the studied drug and its metabolites, and those of the members of library of drugs or other small molecules for which information about their biological counterparts (proteins) is known. The underlying principle is that if a drug or ligand interacts with particular proteins, other drugs or ligands showing a similar pharmacophoric pattern will have a high probability of interacting with the same proteins. This strategy requires the development and maintenance of a large library of ligands with intensive annotation of their biological counterparts (task 4.1 will provide input for this library). The pharmacophoric patterns of drugs inform about their interaction capabilities with biological counterparts and can be coded as numeric vectors. The agreement between pairs of numeric vectors will be measured by means of distances or similarity coefficients. It has to be pointed out that this task requires the implementation of software allowing the computational detection of the potential metabolites of the considered drug.

This task will be led by UPF with major contribution from AZ and USC.

4.3 Ligand-Target Simulations

An alternative procedure for connecting drugs with adverse events is the *in silico* simulation of the interaction of the molecular structure of the studied drug with that of proteins that are known to be anti-targets responsible of particular drug adverse events. This approach implies the development of structural models for the selected proteins (when, as it happens in most the cases, they are not experimentally available), as well as the detailed characterisation of their ligand binding sites. The selection of a limited number of anti-target proteins is forced by the huge effort required for having quality models for them. The existence of inter-individual genetic variations that can affect the structural features of the considered proteins will be also taken into account.

This task will be led by UPF with contribution from AZ and USC.

4.4 Drug-Target-Pathway-Adverse Event Mapping

By mapping the pair-wise relationships resulting from the previous tasks with the state-of-the-art knowledge on biological pathways (which incorporates targets and anti-targets as their nodes), a global entity mapping will result, providing possible paths connecting the tentative drugs and the adverse advents that constituted the output signals of WP3. Regarding the biological pathways, the aim is not only use their publicly available descriptions, but to enrich them with additional protein-protein interactions resulting from literature mining or *in silico* predictions.

This task will be led by AZ, with UPF contribution.

In all of WP4, UPF will be assisted by its subcontractors as appropriate.

Deliverables

D4.1 Report on the Mining of Pharmacological Databases and Repositories. (Month 15)

Halfway through task 4.1, this report will provide details on mining of pharmacological databases and repositories, including software and algorithms developed for that purpose.

D4.2 Description of Ligand-Based Approaches. (Month 21)

This deliverable will comprehensively describe the methods used and results obtained, including software developed, from task 4.2.

D4.3 Report on Ligand-Target Simulations. (Month 25)

This deliverable will comprehensively describe the methods used and results obtained from task 4.3.

D4.4 Report on Literature and DB Mining. (Month 30)

Complete report with details on the results of the literature and DB mining activity, including software and algorithms developed for that purpose.

D4.5 Report on Drug-Target-Pathway-Adverse Event Mapping. (Month 30)

This deliverable will comprehensively describe the methods used and results obtained, including software, from task 4.4, resulting in a substantiation of the signals generated in WP3 according to the available biomedical knowledge.

Work package number	5		**Start date or starting event:**		10		
Work package title	System Integration						
Activity type	RTD						
Participant number	1	3	**4**	5	6	9	10
Participant short name	EMC	UPF	**UAVR**	NEUROLESI	UB2	AZ	UNOTT
Person-months per beneficiary	32	8	**40**	8	8	16	8

Objectives

(a) To integrate the evidence obtained from WP3 and WP4.

(b) To develop a computerised adverse event detection system that integrates the different software components resulting from WP3 and WP4 and adds a web interface for seamless access to the knowledge created by the project.

Description of work

This work package is divided into two tasks.

5.1 Evidence Combination

A framework will be developed to combine evidence from different sources, notably the ranked signal list that results from the signal generation stage (WP3) and the various types of supporting or discounting evidence from the signal substantiation stage (WP4). The evidence combination scheme should be both transparent by offering the end users of the system insight in the way the different sources of evidence are combined, and flexible by allowing users to adjust the weighting of evidence according to their wishes.

This task will be led by AZ with contributions from EMC and UPF, who lead WP3 and WP4 respectively. Participants NEUROLESI, UB2 and UNOTT, who have expertise in signal assessment and false-positive reduction, will also contribute to this activity, together with and UAVR to ensure compatibility with the technical infrastructure.

5.2 Technical Infrastructure

The technical infrastructure will integrate the data and software components developed in WP3 and WP4 into a web-based adverse event detection system (ALERT web).

The primary input of the system consists of the signals that will be generated from the different EHR systems participating in the project (result of WP3). The input data will be submitted according to the standard ontology adopted in WP2. These signals should trigger the various software components developed in WP4 that generate supportive or discounting evidence to re-rank the signal list following the evidence combination scheme. The system should allow the inspection of the signals and the supporting biomedical evidence, and offer different filtering options to focus on specific (classes of) drugs and events. Information on the underlying EHR data sources, biomedical knowledge and contact information should be available. The system should be designed as an open framework that is able to incorporate other external EHR databases in the future, and dynamic so as to access complementary public biomedical resources that can complement the ADR information gathered during the project. Depending on the user profiles (to be defined), the ALERT web will offer several features that can be generically grouped as searching, statistics, reports and

graphs.

This activity will be led by UAVR, who has wide experience in web-based applications, graphical interface design and system integration, and will be executed in close collaboration with EMC.

Deliverables

D5.1 Interim Report on Evidence Combination. (month 21)

Halfway through task 5.1, this deliverable will describe the draft framework developed to combine the evidence on ADR arising from the intermediate results of WP3 and WP4.

D5.2 ALERT System Software Version 1. (month 24)

This deliverable will comprise the web-accessible ALERT system with basic functionality.

D5.3 Final Report on Evidence Combination. (month 33)

This deliverable will describe the final framework developed to combine the evidence on ADR arising from WP3 and WP4.

D5.4 Final Version of the ALERT System Software. (month 36)

This deliverable will comprise the final web-accessible ALERT system with full functionality.

Work package number	6			**Start date or starting event:**			13							
Work package title	System Validation													
Activity type	RTD													
Participant number	1	3	4	**5**	6	7	8	9	10	11	12	13	14	15
Participant short name	EMC	UPF	UAVR	**NEUROLESI**	UB2	LSHTM	AUH-AS	AZ	UNOTT	UNIMIB	ARS	PHARMO	PEDIANET	USC
Person-months per beneficiary	6.9	5.8[a]	2.9	**20.7[b]**	6.9	5.8[c]	6.9	2.9	10.9	6.9	6.9	6.9	6.9	6.9

Objectives

a) To iteratively perform retrospective validation of the ALERT system.

b) To iteratively perform prospective validation of the ALERT system.

Description of work

The ALERT project will follow an iterative development cycle, by which the system will run through several cycles of development during the project life. After each development iteration, validation studies will be performed, the results of which will be fed back into development for improvement and fine-tuning of the system's capabilities. This WP includes two tasks.

6.1 Retrospective validation

The retrospective validation of the ALERT system will be performed by using the validation test sets produced in WP2. The system's ability to rediscover drug-event combinations from the test set with established adverse effects will provide an indication of the sensitivity of the system. The system's ability not to signal drug-event combinations from the test set with spurious signals will provide an indication of the specificity of the system. Since the EHR systems will not be involved in defining the validation sets, all EHR data can be used for retrospective testing purposes. By using a time-dependent retrospective approach, the results of the system will be compared with those based on spontaneous reporting data, to assess the system's capability to provide faster and more precise discovery of ADRs. Examples will be defined in WP2 but may comprise rofecoxib and myocardial infarction, cerivastatin and rhabdomyolisis, and fluoroquinolones and tendon disorders. Spontaneous reporting systems to be used include the French and Italian (Gruppo Interregionale di Farmacovigilanza) pharmacovigilance databases, as well as the WHO spontaneous reporting database. The retrospective validation exercise will also serve to provide measures of economic impact of ALERT.

This task will be led by UNOTT in close co-operation with NEUROLESI. All other participants that have experience in generating and evaluating signals (EMC, UB2, AUH-AS, UNIMIB, ARS, PHARMO, PEDIANET, USC, together with subcontractors as appropriate) will contribute to this task.

6.2 Prospective validation

A prospective evaluation will be done by investigating the top-ranking signals generated by the

[a] Of which 2.9 person-months correspond to subcontractor TAU.
[b] Of which 6.9 person-months correspond to subcontractor SIMG.
[c] Of which 2.9 person-months correspond to subcontractor ICL.

system. For the verification of these top-ranking signals, traditional hypothesis testing approaches, including pharmaco-epidemiological studies using EHR databases, will be followed.

The system's capabilities to support the verification process by providing access to underlying data sources and relevant literature will be assessed. To get an unbiased estimate of the performance of the system, we will use a holdout method in which part of the EHR data will be used for signal generation and the remaining part will be available for validation. Special attention will be given to patient groups that are not routinely involved in clinical trials, for ethical or practical reasons, e.g. pregnant women, elderly people, people using many drugs simultaneously, and in particular children. Finally, the top-ranking signals will be compared with data from spontaneous reporting systems to evaluate the ability of the newly developed system in early and effective signal detection.

This activity will be led by NEUROLESI. All other partners, except FIMIM, will be involved in the prospective validation of signals.

Deliverables

D 6.1 Interim Report on Retrospective Validation. (month 27)

Report on the partial results obtained from the retrospective validation exercise, assessing the performance of the ALERT system version 1.

D 6.2 Interim Report on Prospective Validation. (month 30)

Report on the partial results obtained from the prospective validation exercise, assessing the performance of the ALERT system version 1.

D6.3 Final Report on Retrospective Validation. (month 39)

Report on retrospective validation of the final ALERT system, which will be performed using validation test sets.

D 6.4 Final Report on Prospective Validation. (month 42)

Report on prospective validation of the final ALERT system, which will be performed through epidemiologic investigations of databases and comparative analyses of pharmacovigilance databases.

Work package number	7			**Start date or starting event:**			1							
Work package title	Dissemination and Exploitation													
Activity type	OTHER													
Participant number	1	**2**	3	4	5	6	7	8	9	10	11	12	13	14	15
Participant short name	EMC	**FIMIM**	UPF	UAVR	NEUROLESI	UB2	LSHTM	AUH-AS	AZ	UNOTT	UNIMIB	ARS	PHARMO	PEDIANET	USC
Person-months per beneficiary	3.7	**11.7**	2.6[a]	0.9	3.4[b]	1.7	1.8[c]	0.9	3.7	1.7	1.7	1.7	1.7	1.7	0.9

Objectives

(a) To design a plan that allows for optimal communication within the project and the dissemination of information and knowledge generated by the project to relevant stakeholders.

(b) To design and deploy the tools that will be needed to implement the plan.

(c) To undertake extensive dissemination activities according to the communication plan.

(d) To devise exploitation scenarios aiming at ensuring sustainability of the ALERT system after the EC funding period.

Description of work

This work package comprises three main activities.

7.1. Communication Plan and Tools

This activity will focus on the development of a Communication Plan for raising awareness of the project and its results among different stakeholders. Before undertaking the dissemination activities, it will be necessary to design a consistent strategy that allows for maximizing the impact of the communication efforts.

This plan will be set up on the four basic pillars of the communication strategy:

i) Definition of the dissemination objectives;

ii) Identification of the relevant target audiences;

iii) Description of the dissemination actions to be tackled;

iv) Identification of the specific tools to be developed in order to support effective communication.

Once the Communication Plan has been set up, the communication tools (such as project website, newsletter, brochure, templates, etc.) identified in the plan will be developed, keeping in mind the actions, audiences and objectives to which these tools should serve as supporting materials. For example one of the communication tools would be an electronic newsletter that allows ALERT stakeholders to be informed about the project main developments. A project web page will be set up at an early stage in the project.

A specific protocol for the generation of high-quality scientific publications will be established. The protocol will include review and authorship policies.

[a] Of which 1.7 person-months correspond to subcontractor TAU.
[b] Of which 1.7 person-months correspond to subcontractor SIMG.
[c] Of which 0.9 person-months correspond to subcontractor ICL.

The activity has an extended time schedule to provide for updates of the communication tools as needed during the first stages of the project.

This activity will be led and executed by FIMIM.

7.2. Dissemination Activities

This activity will organize, implement and coordinate the dissemination actions addressed to make available to the target audiences information on, and arising from, the project. The starting point will be the Communication Plan developed in 7.1, which will define the kind of activities that should be undertaken to reach the audiences more efficiently, and provide the tools for doing so.

Dissemination activities are expected to have mainly a scientific nature (articles, presentations at conferences, etc.), but, increasingly as the project unfolds, specific contacts and presentations to foreseen end-users of the project results (regulatory agencies, pharmaceutical companies, database owners, healthcare institutions and professionals, academia) will be implemented as needed. Such activities will be regularly reported at the time of the management and periodic reports, as well as in specific intermediate and final reports on dissemination activities. Appropriate review and information procedures will be set up within the Consortium to allow for overall coherence and awareness on the dissemination activities undertaken.

ALERT will participate in regular concertation activities (at least two per year) with other ICT projects, which will be organised to facilitate exchange of information and good practice and to discuss topics of common interest to all relevant projects and/or other relevant stakeholders. Particular attention will be given to establish contacts with the EMEA during the activities of the project.

All participants are expected to contribute to this activity.

7.3. Exploitation

This activity will be executed during the last year of the project, and it will be centered on studying different sustainability scenarios for long term maintenance and development of the ALERT system. The different intervening, relevant actors in the field addressed will be actively encouraged to participate in debates organized by the project. Although the initial expectation is that ALERT should become an open, primary tool for use by regulatory authorities in Europe, other stakeholders (e.g. pharmaceutical companies, database owners/producers, academia undertaking research on ADRs, etc.) will have to be engaged in order to secure enlargement (and thus, increasing added value and benefits) and maintenance of the system in the longer term. This activity will benefit from the results of the validation tasks in WP6, insofar as those are expected to prove the added value of the system and promote the interest of key stakeholders, especially for what refers to measures of the economic impact. Careful consideration of both background and foreground, and any IPR issues, using input from activity 8.3, will be an important asset for the development of this activity.

This activity will carried out by EMC, FIMIM and AZ.

Deliverables

D7.1: Communication Plan. (month 6)
A plan for dissemination that includes the communication objectives, target audiences, activities to be carried out and tools that will support their implementation, with connections among these components.

D7.2: Report on the ALERT Communication Tools. (month 12)

This deliverable will describe in detail the communication tools developed in the framework of the project. It will include description of a project web page up and running.

D7.3: Intermediate Report on Dissemination Activities. (month 24)
A detailed list of dissemination activities carried out halfway through the project, with assessment of their impact, degree of compliance with the plan, and future dissemination activities expected.

D7.4: Final Report on Dissemination Activities. (month 42)
A detailed list of dissemination activities carried out halfway through the project, with assessment of their impact, degree of compliance with the plan,

D7.5: Report on Exploitation and Sustainability Plans. (month 42)

This deliverable will describe the exploitation scenarios envisaged by the project in order to ensure long term sustainability, including SWOT analysis of each of the possibilities. Contacts held with stakeholders and assessment of IPR issues that may be encountered will be reported in this deliverable as well.

Work package number	8	**Start date or starting event:**		1		
Work package title	Project Management					
Activity type	MGT					
Participant number	1	**2**	3	4	5	6
Participant short name	EMC	**FIMIM**	UPF	UAVR	NEUROLESI	UB2
Person-months per beneficiary	4.9	**41.3**	2.5	2.5	2.5	2.5

Objectives

(a) To set-up a project management structure that ensures an efficient operational management including administrative, financial and legal issues.

(b) To ensure that the project is appropriately managed according to the work plan, supporting the Scientific Coordination in organising and supervising the work and in its liaison with the European Commission.

(c) To comprise resources, procedures and tools for ensuring that all results are delivered on time, with an adequate quality level and within cost, comprising risk management and quality control procedures on deliverables.

(d) To support the appropriate communication and work dynamics to help drive the whole Consortium as a team towards successful completion.

Description of work

Project Management in ALERT is deeply connected to WP1 – Scientific Co-ordination as a central piece of the global management structure of the project. Three main tasks are included in this work package, directly related with major areas in project management that will need due attention.

8.1. Day-to-day Management

This activity is essentially devoted to co-operate with and provide support to the Scientific Co-ordination and the overall management structure (especially WP Leaders) in:

- Liaison with the European Commission.
- Work plan control and update, linkage of project components, schedule control.
- Risk management.
- Timely submission of deliverables with appropriate quality levels.
- Decision making, conflict resolution and consensus building.
- Promotion of synergy and efficiency throughout.
- Easing communication among partners. Enabling of tools for efficient communication and co-operative work among partners.
- Support to meetings organization and meeting minutes production. Implementation of derived actions into the work plan, and follow-up.

This activity will comprise risk management. This will entail identification, assessment and follow-up of threats and opportunities. Following a bottom-up approach, risks will be identified in co-operation with all Work Package Leaders, and assessed using a simplified system of two variables (*impact, probability*), each of them measured in a three-point scale ranging from 1-Low to 3-High. A relevance index will be constructed for each risk multiplying both variables, so that the Consortium can prioritise risks and focus on the most relevant ones (typically, indexes equal or greater than 4). Essential characteristics of each risk will be defined (description, trigger event,

owner, etc.). Actions addressed to affect probability and/or impact before the risk happens (*mitigation plans*) will be defined for priority risks, and actions to be carried out if the risk happens (*contingency plans*) will be devised as well. The risk registry will be maintained, and procedures for incorporating risks that happen (*issues*) into the work plan, and managing out risks, will be designed.

Management of quality control procedures on deliverables and other project results is also envisaged in this activity. Different in nature to the quality assurance activities envisaged in WP1, this task refers to ensuring that deliverables adhere to some quality principles (such as completeness, relevance, uniformity in presentation, etc.) making them suitable for submission to the Commission. Procedures for achieving this (such as peer-review) will be set up.

Partner FIMIM will be responsible for this continuous task.

8.2. Reporting and Administration

This activity will be devoted to:

- Financial management: cost control and justification, budget management, EC contribution distribution control (supporting the contractual obligations of the Project Coordinator). Budget assignment is expected to be somewhat flexible and help steer efforts in the most productive way; for that, specific, transparent procedures will be included in the Consortium Agreement.
- Periodic Reporting: setting up of reporting mechanisms, providing education and support to partners in appropriate reporting, including facilitation of the task via web-based systems as needed.

Reporting and administration is usually one of the main areas of difficulty for partners, and in a project with a significant Consortium size, it can create an enormous overhead that hampers the project's progress; thus, it is especially important that partners are at all times aware of important determinants of reporting and finances (including the provision of audit certificates, certificates on methodology, etc.), that the processes involved are closely monitored, and that partners get bilateral support to avoid any distortions in the work flow. This will ensure timely delivery of the required reports to the Commission. All these tasks will be reinforced by giving them appropriate visibility in Consortium meetings. Special attention will be paid to the correlation between effort reporting and cost justification, and to help partners manage the relationships between financial flows (budget, funding, justification, expenditure, payments). Support to the whole Consortium regarding the implementation of subcontracting and incorporation of third parties in general will also be accounted for.

This activity will be carried out by FIMIM, with contributions from all Work Package Leaders, and run through the whole project.

8.3. Contract and Legal Management

This task will deal with all contractual and other legal issues related to the project. In particular, it will comprise Grant Agreement and Consortium Agreement implementation and amendments, and the related procedures. It will also entail partnership management (especially regarding relationships with subcontractors and external collaborators) and formalising updates of the work plan, roles and resources assignment as needed. Additionally, support to global knowledge management in the Consortium will be provided. Aside from easing brokerage of knowledge offers and demands within the Consortium for efficient execution of the work plan, this will also entail IPR management, in connection with the provisions of the Consortium Agreement. Both background used and foreground generated in the framework of the project will need to be identified, and access rights appropriately managed so that scientific work can develop without any

obstacle. For this purpose, support to appropriate definition of ownership of the results, and identification of exploitation scenarios (in connection with activity 7.3) will be facilitated. Results of these tasks will be periodically reported in dissemination and use plans and/or annual progress reports as required by the Grant Agreement provisions.

This activity will be carried out by FIMIM during the whole project.

Deliverables

D8.1: Project Handbook. (month 3)

This deliverable will summarise in understandable language some of the key provisions in the Consortium Agreement and the Grant Agreement, to serve as a quick reference for partners. It will also explain the Consortium organizational structure, decision-making procedures, roles and responsibilities, internal communication policy and quality control and risk management procedures.

D8.2: Technical and Financial Annual Reports #1. (month 12)

D8.3: Technical and Financial Annual Reports #2. (month 24)

D8.4: Technical and Financial Annual Reports #3. (month 42)

These will be the official reports to be sent to the Commission at regular intervals, following the corresponding EC guidelines for reporting. In particular, these will include:

- Periodic Reports as specified in Annex II to the GA, article II.4.1.

- Final Report as specified in Annex II to the GA, article II.4.2 (including the Final plan for the use and dissemination of foreground).

- Report on the distribution of the Community financial contribution between beneficiaries, as specified in Annex II to the GA, article II.4.3.

- Certificate on the financial statements as specified in Annex II to the GA, article II.4.4.

B 1.3.6 Efforts for the full duration of the project

Project number (acronym): 215847 (ALERT)

Work package	WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8	TOTAL per Beneficiary
Beneficiary 1 - EMC	**14.1**	1.7	**54.7**	14.8	32.0	6.9	3.7	4.9	132.8
Beneficiary 2 - FIMIM	6.3						**11.7**	**41.3**	59.3
Beneficiary 3 - UPF	2.3	1.7		**64.1**	8.0	5.8	2.6	2.5	87.0[a]
Beneficiary 4 - UAVR	2.3				**40.0**	2.9	0.9	2.5	48.6
Beneficiary 5 - NEUROLESI	3.8	11.7	27.3	7.4	8.0	**20.7**	3.4	2.5	84.8[b]
Beneficiary 6 - UB2	2.3	**11.7**		7.4	8.0	6.9	1.7	2.5	40.5
Beneficiary 7 - LSHTM		3.4	13.0	7.4		5.8	1.8		31.4[c]
Beneficiary 8 - AUH-AS	1.5	1.7	22.5			6.9	0.9		33.5
Beneficiary 9 - AZ				41.9	16.0	2.9	3.7		64.5
Beneficiary 10 - UNOTT	1.5	1.7	22.5		8.0	10.9	1.7		46.3
Beneficiary 11 - UNIMIB	1.5	1.7	22.5			6.9	1.7		34.3
Beneficiary 12 - ARS	1.5	1.7	22.5			6.9	1.7		34.3
Beneficiary 13 - PHARMO	1.5	1.7	27.3			6.9	1.7		39.1
Beneficiary 14 - PEDIANET	1.5	1.7	27.3			6.9	1.7		39.1
Beneficiary 15 - USC				17.1		6.9	0.9		24.9
TOTAL	**40.1**	**40.4**	**239.6**	**160.1**	**120.0**	**104.2**	**39.8**	**56.2**	**800.4**

[a] Of which 13.7 person-months correspond to subcontractor TAU.
[b] Of which 39.1 person-months correspond to subcontractor SIMG
[c] Of which 12.0 person-months correspond to subcontractor ICL.

Project Effort Form 2 - indicative efforts per activity type per beneficiary
Project number (acronym): 215847 (ALERT)

Activity Type	1 EMC	2 FIMIM	3 UPF	4 UAVR	5 NEUROLESI	6 UB2	7 LSHTM	8 AUH-AS	9 AZ	10 UNOTT	11 UNIMIB	12 ARS	13 PHARMO	14 PEDIANET	15 USC	TOTAL ACTIVITIES
RTD/Innovation activities																
WP1: Scientific Coordination	**14.1**	6.3	2.3	2.3	3.8	2.3		1.5		1.5	1.5	1.5	1.5	1.5		40.1
WP2: Standards	1.7		1.7		11.7	**11.7**	3.4	1.7		1.7	1.7	1.7	1.7	1.7		40.4
WP3: Signal Generation	**54.7**				27.3		13.0	22.5		22.5	22.5	22.5	27.3	27.3		239.6
WP4: Signal Prediction:	14.8		**64.1**		7.4	7.4	7.4		41.9						17.1	160.1
WP5: System Integration	32.0		8.0	**40.0**	8.0	8.0			16.0	8.0						120.0
WP6: System Validation	6.9		5.8	2.9	**20.7**	6.9	5.8	6.9	2.9	10.9	6.9	6.9	6.9	6.9	6.9	104.2
Total 'research'	**124.2**	**6.3**	**81.9**	**45.2**	**78.9**	**36.3**	**29.6**	**32.6**	**60.8**	**44.6**	**32.6**	**32.6**	**37.4**	**37.4**	**24.0**	**704.4**
Consortium management activities																
WP8: Project Management	4.9	**41.3**	2.5	2.5	2.5	2.5										56.2
Total ' management'	**4.9**	**41.3**	**2.5**	**2.5**	**2.5**	**2.5**										**56.2**
Other activities																
WP7: Dissemination & Exploitation	3.7	**11.7**	2.6	0.9	3.4	1.7	1.8	0.9	3.7	1.7	1.7	1.7	1.7	1.7	0.9	39.8
Total 'other'	**3.7**	**11.7**	**2.6**	**0.9**	**3.4**	**1.7**	**1.8**	**0.9**	**3.7**	**1.7**	**1.7**	**1.7**	**1.7**	**1.7**	**0.9**	**39.8**
TOTAL BENEFICIARIES	**132.8**	**59.3**	**87.0**[a]	**48.6**	**84.8**[b]	**40.5**	**31.4**[c]	**33.5**	**64.5**	**46.3**	**34.3**	**34.3**	**39.1**	**39.1**	**24.9**	**800.4**

[a] Of which 13.7 person-months correspond to subcontractor TAU.
[b] Of which 39.1 person-months correspond to subcontractor SIMG.
[c] Of which 12.0 person-months correspond to subcontractor ICL.

B 1.3.7 List of milestones and planning of reviews

List and schedule of milestones

Milestone no.	Milestone name	WPs no's.	Lead beneficiary	Delivery date from Annex I [53]	*Comments*
1	Definition of event list	2	6	Month 4	Events defined and submitted as D2.1
2	Completion of validation sets	2	6	Month 4	Validation sets defined and documented, submitted as D2.2
3	Finalisation of standardisation and mapping of terminologies	2	6	Month 9	Map of terminolgies regarding drugs and medical events across EHR databases completed and reported as D2.3
4	Completion of 1st versions of software and algorithms for data extraction and mining of databases and repositories	3,4	1,3	Month 15	Basic functionality of prototype software and algorithms for mining of clinical and biomedical dbs and repositories demonstrated
5	Completion of mid-term assessment of the project	1	1	Month 21	Project explicitly evaluated as regards to fulfilment of its objectives, as reported in D1.3
6	Completion of ALERT system software version 1, including underlying software components	3,4,5	1,3,4	Month 25	Prototype of ALERT web system accessible and running flawlessly with basic functionality, reported as D5.2, including completed underlying software components, documented and reported as D3.1, D3.2, D4.2 and D4.3
7	Finalisation of an evidence combination framework	5	4	Month 33	Combination framework documented and reported as D5.3

[53] Month in which the milestone will be achieved. Month 1 marking the start date of the project, and all delivery dates being relative to this start date.

8	Completion of final version of the ALERT System software, including underlying software components and algorithms	3,4,5	1,3,4	Month 36	Prototype of final ALERT web system running flawlessly with full functionality, reported as D5.4, including completed underlying software components and algorithms for data and literature mining, pathway mapping, etc. documented and reported as D3.3, D4.4 and D4.5
9	Completion of retrospective validation studies	6	5	39	Results from retrospective validation documented and reported as D6.3
10	Completion of prospective validation studies	6	5	42	Results from prospective validation documented and reported as D6.4
11	ALERT Project completion	1,8	1,2	42	All other milestones achieved and final report submitted

Tentative schedule of project reviews

Note: This is a new table which was not included in the proposal.

Tentative schedule of project reviews			
Review no.	**Tentative timing, i.e. after month X = end of a reporting period** [54]	***planned venue of review***	***Comments , if any***
1	After project month: 12	**Brussels**	
2	After project month: 24	**Brussels**	
3	At project month: 42	**Brussels**	

[54] Month after which the review will take place. Month 1 marking the start date of the project, and all dates being relative to this start date.

B2. Implementation

B 2.1 Management structure and procedures

The characteristics of the ALERT project, both in effort and budget terms, and also in relation with its ambitious objectives and the diversity of participants involved, makes it a complex activity to manage. The Consortium is constituted by twelve partners belonging to eight European Member States, with a significant number of subcontractors. The management structure has been envisaged to respond to the needs of a medium-scale focused research project (STREP), but taking into account that the size of the initiative is above average and the time schedule is tight considering the achievements and impact expected from the project, thus leading to an iterative development approach in which tasks often run in parallel. Consequently, the organisational structure is built on both traditional management principles but also on an ad-hoc structure adapted to the particular characteristics of the project. This structure aims to ensure efficiency and at the same time avoid imposing an exaggerated overhead to the project, what might damage its scientific and technical progress.

The management structure proposed for ALERT is therefore based on a multi-level organisation that balances:

- the fulfilment of the work plan *per se.*
- the management of trade-offs affecting scope, quality, time and cost.
- the due attention needed on critical activities that aim to ensure the achievement of milestones and that contribute to strategic objectives (such as community outreach).
- the relationships among partners, including conflict resolution.
- the quality and efficiency with which the project activities are carried out.
- the proper follow-up and fulfilment of the grant agreement with the Commission, including administrative and financial issues.

THE MANAGEMENT STRUCTURE

Management of the ALERT Project at the operational level will be a responsibility of partner FIMIM, centred on WP8. FIMIM has a wide experience in managing and co-ordinating European projects since FP4, with special emphasis on multidisciplinary undertakings of significant size.

Project Management will also be bonded with strong Scientific Coordination (WP1), which will be responsibility of the Project Co-ordinator at the Erasmus University Medical Center (EMC). This tandem of solid Scientific Leadership and professional Project Management is devised as the main driver for the project, allowing the scientific strategic direction and coordination to be undertaken without the distortions that the overhead derived from legal, administrative and financial procedures impose on a project of these characteristics. Conversely, it also allows project management to be carried out with high efficiency and professionally, without the limitations that may be imposed by good scientific relationships with partners, otherwise necessary for the creation of adequate communication and work dynamics. Both FIMIM and EMC have collaborated closely in the recent INFOBIOMED Network of Excellence, and the dual leadership structure has been tried and tested for several years in different projects with excellent results.

Taking into account all of the abovementioned, a management structure has been designed with the following components:

- **General Assembly (GA)**: A body gathering all partners in the project, including subcontractors, in charge of overseeing the project's progress and facilitating global collaboration among all participants.
- **Steering Committee (SC)**: An executive body comprising Work Package leaders, including the Scientific Co-ordinator and the Project Manager, plus partners UNOTT and AZ, with decision powers on technical development, work plan updates, and effort and budget re-assignment.
- **Scientific Co-ordination (SciC)**: A key role in charge of the global scientific leadership, quality assurance policy and assessment of the project.
- **Project Management (PM)**: A management team set up for daily management of the project.
- **Scientific Advisory Board (SAB)**: A consultative body assisting the Steering Committee for scientific and technical matters.
- **Work Package Leaders (WPL)**: Leading participants of each work package.

This structure will be complemented if necessary with ad-hoc Committees set up to deal with issues that require particular attention or expert advice through the project's development (e.g. ethical issues). *Figure 4* shows how the components in the management structure are inter-related. The structure covers three essential management 'areas'; the first is related to actual **work**, represented at the lower level by partners contributing to each activity; the second refers to **co-ordination**, including Work Package Leaders, Scientific Co-ordination and Project Management components; the third deals with **review and approval**, and comprises the Scientific Co-ordination/Project Management units, the Steering Committee, the Scientific Advisory Board and other Committees, and the General Assembly.

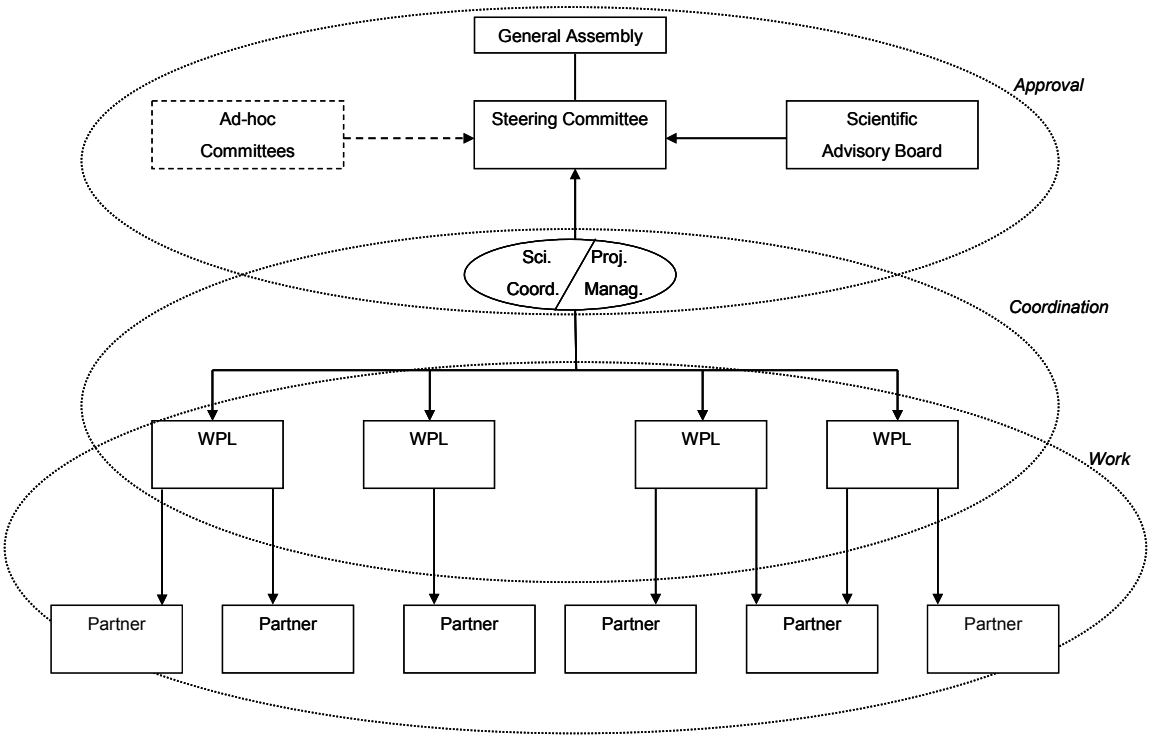


Figure 4: Management structure in the ALERT project.

- **General Assembly (GA)**

Representing in essence the whole Consortium, but adding also the subcontractors, the General Assembly will oversee the project's progress and provide a forum for general discussion on the strategic orientation and development of the project, enhancing mutual knowledge and co-operation among participants. The GA will also intervene for those decisions that following EC rules require a unanimous decision of the Consortium (in which cases, each partner will be allocated one vote; subcontractors will have voice but not vote). General Assembly meetings will be regularly held (at least every six months), so that the project evolution and governance are visible and transparent for all participants, and contributions are timely gathered and discussed.

- **Steering Committee (SC)**

A Steering Committee will be established consisting of a representative from each of the Work Package Leaders, thereby including the Project Manager, plus partners UNOTT and AZ, which lead key activities, and chaired by the Scientific Co-ordinator. Therefore, the SC will be initially formed by: Johan van der Lei (EMC), Carlos Díaz (FIMIM), Nicholas Moore (UB2), Ferran Sanz (UPF), José Luis Oliveira (UAVR), Gianluca Trifirò (NEUROLESI), Julia Hippsley-Cox (UNOTT) and Scott Boyer (AZ). Members of the SC will be required to have the authority to take corrective actions as necessary within their respective organisations, or clarify the relevant line management. The SC will be responsible for decisions regarding the overall technical strategy of the project. Changes in the work plan, partnership composition and resource allocation will also be a prerogative of the SC, except for decisions that have to be unanimous within the Consortium following the Grant Agreement provisions and/or EC rules. In those cases, the SC will summarise pending issues regularly and look for approval of all partners, preferably in GA meetings if the timing allows so. The SC will monitor and review progress, ensure that objectives are met and approve deliverables. For these purposes, the SC will meet at least every three months, either face-to-face, via internet or tele-conferences.

The SC will be allowed to require specific actions or reports from the PM and/or WPL in order to solve any issues that cannot be clarified or agreed at a lower level. These include in particular the resolution of disputes and matters relating to allocation of funding, as well as situations in which the project efficiency might be endangered. At the initiative of any of its members, the SC will also be able to constitute committees for matters that require specific attention, and to establish working procedures for such committees. In particular, and depending on the early outcome of task 1.3, a Clinical data and Ethics Committee may be set up with participation of all the clinical databases owners/managers (EMC, AUH-AS, UNOTT, UNIMIB, ARS, PHARMO, PEDIANET, and subcontractor SIMG), plus an independent legal advisor (see SciC below). For decision purposes, each member of the SC will be allocated one vote. Two thirds of the participants attending a meeting of the SC will constitute a quorum. Simple majority of the attendants will be enough for decision adoption. In the event of a tied vote, the Scientific Co-ordinator (as chair) will have an additional vote. In all of its activities, the SC will be assisted by the PM and a Scientific Advisory Board, as well as by any committees created for specific purposes.

- **Scientific Co-ordinator (SciC)**

As Chair of the SC, the Scientific Co-ordinator will be responsible of overall scientific leadership of the project in order to ensure that the work is technically performed according to the overall strategy. He will provide strategic guidance, devise changes in scoping and focus of the different tasks, co-ordinate all efforts of WPL and manage dependencies between tasks,

linking the project components towards a successful completion. He will be a central figure for conflict resolution, decision-making enabling and consensus building, supported by the PM. He will also coordinate the participation of the SAB and any other ad-hoc Committees as needed, and be in charge of promoting the definition of high quality standards applicable throughout the work plan, directing the efforts towards assessment and validation of the project. Importantly, the Scientific Co-ordinator will be responsible for monitoring all ethical issues in the project. For this role, he will also be assisted by an independent legal advisor so that all legal issues pertinent to ethics (including data protection) are appropriately dealt with. The SciC will regularly receive input from WPL on all ethical issues arising as the work unfolds, and will directly supervise all clinical databases in the Consortium in the framework of task 1.3 – where all such databases have been allocated effort.

- **Project Management (PM)**

A Project Management office will be set, which will follow-up activities and monitor compliance with the work plan, planned resources and time schedule. It will also provide close support to the Scientific Coordination, including appropriate liaison with the European Commission. The PM will also support WP leaders in day-to-day management, promoting synergy and efficiency throughout. It will facilitate communication among partners, ensuring timely delivery of the project deliverables and tracking milestone achievements.

The PM will also drive risk management (identification, assessment of threats and opportunities, mitigation and contingency plans), and will manage quality control procedures on deliverables. It will deal with partnership management (accession of new partners, withdrawal, relationships with external collaborators), Grant Agreement and Consortium Agreement management (amendments, subcontracts, third parties) and other legal issues. It will closely co-operate with the SciC and WPL in periodic reporting. The PM will be responsible of overall financial management (cost control and justification, budget management, payments control), supporting the SC in budget re-arrangements, and coordinating and supporting all partners in financial and administrative tasks. It will also co-ordinate global knowledge management. Finally, it will support meetings organisation both at the SC and GA levels, and the production of the corresponding minutes. For the development of these tasks, the PM office will initially benefit from the involvement of a Project Manager, a Project Assistant, a Financial Manager and a Communication and Exploitation Manager (who will have specific responsibility in clarifying IPR issues), who will dynamically contribute to the project as the need arises. Other roles may be added according to the needs of the project regarding specific issues.

- **Scientific Advisory Board (SAB)**

A Scientific Advisory Board will be formed with participation of leading figures in relevant fields, who will be external to the project, providing a consultative function in order to assist the SC on scientific and technical grounds when needed. SAB members will be asked to sign an agreement to ensure confidentiality. There will be three permanent SAB members, and the rest of the SAB will be conformed by a pool of international experts, who will be selectively called during the project's development depending on the issue to be discussed. Representation of safety experts and regulatory authorities in the SAB will be ensured at all times, and representatives of both Dutch and Spanish regulatory authorities have already agreed to be members of the SAB. Special care will also be taken to invite ethics experts as needed (particularly in the light of the issues that can arise from the analysis carried out early on in the project and included in deliverable 1.1). The SAB will normally meet once a year

and, if needed, decision making procedures will follow the same voting mechanisms as in the SC. Confirmed members of the SAB are:

- Sabine Straus, MD, PhD - Head of Pharmacovigilance of the Dutch Medicines Evaluation Board.
- Francisco J. de Abajo, MD, PhD, M.P.H. - Head, Division of Pharmacoepidemiology and Pharmacovigilance, Spanish Medicines Agency.
- Fernando de Andrés-Trelles, MD, PhD - Member of the Spanish Medicines Evaluation Board (previously Chairman). Member of the Scientific Advice Working Party (SAWP) and the Patients and Consumer organizations Working Party (PCWP) of the European Medicines Agency (EMEA).
- Jan H. van Bemmel, MSc, PhD - Professor of Medical Informatics at Erasmus University Rotterdam, editor-in-chief of Methods of Information in Medicine, of IMIA Yearbooks of Medical Informatics, and of the Handbook of Medical Informatics.
- Alexander Walker, Dr.P.H. - Adjunct Professor of Epidemiology, Harvard School of Public Health, Harvard University.
- Yola Moride, M. Sc. (Génétique), Ph. D. (Epidémiologie & Biostatistiques) - Professeure agrégée, Université de Montréal.

- **Work Package Leaders (WPL)**

Each work package is the responsibility of one participant, who will act as Work Package Leader. The WPL will ensure day-to-day management and co-ordination of the activities included in their respective work packages. WPLs will implement solutions for technical problems, produce the corresponding deliverables, identify risks as early as possible and follow them up, and report to the SciC and PM the progress achieved against that planned. They will be able to raise proposals to the SC regarding effort and budget redistribution, and re-assignment of roles and responsibilities within their respective WPs. WPL will also be responsible of detecting and reporting any ethical issues that might arise during the execution of the project.

This management structure, which will be confirmed in the Consortium Agreement, will be integrated so as to promote smooth and dynamic collaboration between the Project participants. The SC will be the main executive body in the management structure, supported by the SciC / PM tandem, which will steer the project in direct connection with WPLs for day-to-day activities. In general, WPLs will be leading the implementation of the different activities in their respective WPs directly in connection with involved partners, so there is no further organisational level corresponding to activity leadership *per se*. However, there are two exceptions: partners UNOTT and AZ, who, without prejudice of the overall authority of the corresponding WPL, will be leading key activities in the work plan (task 5.1 Evidence Combination and 6.1 Retrospective Validation, respectively). Consequently, and also taking into account the key expertise of both partners, they will be part of the SC together with the WPLs.

The management structure of ALERT has also been designed to help secure both communication and conflict resolution procedures.

As regards to communication, a Consortium communication policy will be established by the PM, making extensive use of electronic resources. A password-protected Intranet structure

will be set up to support management activities, communication and exchange of information among participants. This structure will allow participants to access to the information about the current status of the project and facilitate communication with each other. Online forms for progress reporting will be set up. An appropriate periodicity of face-to-face meetings will be established, so that it helps to propel efforts by friendly peer-pressure. Participants will be encouraged to hold Work Package, Task or topic-specific meetings as necessary for the implementation of the work.

Regarding conflict resolution, the project organisation is devised to support a bottom-up approach. Conflicts amongst participants in any given activity will be solved at the work package level with the help of the respective WPL; if unresolved or in case of conflict of interest, the issue will be raised up to the level of the PM and SciC, who will use mediation and their expert and referent powers to objectively solve the issue. If still unresolved, the issue will in turn be referred to the SC, where voting mechanisms take place. These procedures will be formally agreed upon in the Consortium Agreement. In cases where legal action is needed, the PM will seek to obtain the required authorisation from the Consortium and act accordingly in agreement with the legal documents regulating the development of the project.

B 2.2 Beneficiaries

Participant 1: Erasmus University Medical Center (EMC)
Medical Informatics at EMC is an interdisciplinary research group, studying new methods for acquiring, representing, processing, and managing knowledge and data within health care and the biomedical sciences. Its research clusters around two main themes: structuring of medical data, with the electronic patient record as an important application area, and structuring of medical knowledge, with decision support as main focus. In our research line structuring of medical data we concentrate on the nature and structure of medical data. Ideally, medical data recorded in the context of clinical care should not only be available for patient care, but also be accessible for other purposes, such as scientific research, quality assurance, or management, each usage creating its own demands. Once electronic patient records are available, our research focus shifts to the actual use of the data for multiple purposes. Together with other disciplines we analyze observational databases and study issues involved in naturalistic trials. Concerning medical knowledge we investigate the description of knowledge according to a formal representation so that the knowledge can be made operational in a computer system.

Key personnel
Johan van der Lei, head of the Department of Medical Informatics. His initial research focussed on understanding the requirements for successful introduction of information and communication technology in medical practice. Currently, his interests are on the development, evaluation, use, and impact of computer-based patient records.
Jan Kors, Associate Professor in Medical Informatics. He has a PhD (1992) from the Erasmus University Rotterdam for research on knowledge extraction for automated interpretation of electrocardiograms. His research interests include biosignal analysis and interpretation, machine learning, data and text mining for information extraction and knowledge discovery.
Miriam Sturkenboom, Associate Professor in Pharmacoepidemiology**,** received her PhD degree (cum laude) (1995) and PharmD degree (1995) from the University of Groningen. She received her Master of Science degree from the Harvard School of Public Health in Boston (1996). Her major research interests are in the pharmacoepidemiology field, studying the intended and unintended effects of drugs in large populations, and the use of medical databases to conduct these studies.

Recent publications relevant to the project
- Schuemie M, Chichester C, Lisacek F, Coute Y, Roes PJ, Sanchez JC, Kors JA, Mons B. Assignment of protein function and discovery of novel nucleolar proteins based on automatic analysis of MEDLINE. Proteomics 2007; 7: 921-31.

- Jelier R, Jenster G, Dorssers LC, Wouters BJ, Hendriksen PJ, Mons B, Delwel R, Kors JA. Text-derived concept profiles support assessment of DNA microarray data for acute myeloid leukemia and for androgen receptor stimulation. BMC Bioinformatics 2007; 8: 14.

- Verhamme KM, Mosis G, Dieleman J, Stricker B, Sturkenboom MC. Spironolactone and risk of upper gastrointestinal events: population based case-control study. BMJ 2006; 333:330.
- Verhamme KM, Dieleman JP, Van Wijk MA, van der Lei J, Bosch JL, Stricker BH, Sturkenboom MC. Nonsteroidal anti-inflammatory drugs and increased risk of acute urinary retention. Arch Intern Med 2005; 165: 1547-51.
- Verhamme KM, Bosch RJ, Sturkenboom MC. Finasteride in benign prostatic hyperplasia. N Engl J Med 2004; 350: 1359-61.

Participant 2: Fundació IMIM (FIMIM)

Fundació IMIM (FIMIM) is a private non-profit independent organisation whose objective is to support and manage research at the Municipal Institute for Medical Research (IMIM) in Barcelona. FIMIM has a wide experience in managing and administrating international projects, and particularly European projects. Its Project Office, located at the Research Unit on Biomedical Informatics of IMIM, is a professional structure made up of 5 highly skilled, experienced professionals with expertise on international collaboration and a solid technical background. It is currently co-ordinating the INFOBIOMED NoE (6th Framework Programme, IST priority, eHealth), and has co-ordinated the LINK3D, ELCANO, INFOPHARMA and TESEMED projects in previous FPs. It also participates or has participated as a partner in 5 projects during FP6. The expertise of the Project Office team covers: project management; financial management; legal assessment; exploitation and intellectual property rights management; knowledge management; validation and assessment; business planning; and training, dissemination and communication strategies design and implementation.

Their role in the project will be providing a management structure that both helps and monitors the project development and integration, thus becoming a crucial tool for its success. This main contribution will be in WP8: Project Management. FIMIM will also have a key responsibility as leader of WP7: Dissemination and Exploitation.

Key personnel

Carlos Díaz: University degree in Economy and Business Administration (extraordinary award), Autonomous University of Barcelona 819949. He has a wide experience in the management of Research and Development projects funded by the European Commission and the Spanish and Catalan governments. From 1994 to 1998 he developed his professional activity at the National Microelectronics Centre (CNM-CSIC) as Financial Manager of 26 European projects (ESPRIT, RITE-EURAM, and INCO-DC Programmes). Since 1998 he is EU Projects Manager at Fundació IMIM (Municipal Institute of Medical Research) in Barcelona, carrying out the management and co-ordination of 8 European projects (TAP, INCO, TEN-Telecom, IST programmes), assisting other institutions as well in the co-ordination of LIFE and IST Integrated Projects. He regularly teaches courses on European Projects Management for a wide variety of institutions at the national level. He is currently CEO of Pharmatools Digital Interactive Services S.L., a spin-off based on the results of an FP4 EU project.

Nathalie Villahoz: University degree in Journalism and Social Communication, Universidad del Salvador, Argentina (2001). Since 2004, she has been assisting the EU Projects Manager in different tasks. Project Assistant in the Network of Excellence (INFOBIOMED), responsible of two STREPS and one IP, funded under FP6. She has also managed the Training Node of the Spanish National Institute of Bioinformatics.

Recent publications relevant to the project

- Maojo V, de la Calle G, Martín-Sánchez F, Díaz C, Sanz F. INFOBIOMED: European Network of Excellence on Biomedical Informatics to Support Individualised Healthcare. Proceedings AMIA Symposium 2005: 1041.
- Llargues E, Díaz C, Fito R, Sanz F. Assessing the implementation of the VisualCor software in medical practice. Med Clin (Barc) 2005; 124: 627-9.
- Pastor M, Benedetti P, Carotti A, Carrieri A, Díaz C, et al. Distant collaboration in drug discovery: the LINK3D project. J Comput Aided Mol Des 2002; 16: 809-18.
- Sanz F, Silveira C, Díaz C, Alonso A, Loza MI, et al. Information technology in community pharmacies for supporting responsible self-medication. Am J Health Syst Pharm 2000; 57: 1601-3.
- Sanz F, Gaedt K, Alonso A, Díaz C. New technologies for the marketing and sale of medicines on the Internet and television networks. Final Study. Luxembourg: European Parliament. Scientific and Technological Options Assessment (STOA). Directorate General for Research. 2000 Jan. PE number: PE 168.393/Fin.St.

Participant 3: Universitat Pompeu Fabra (UPF)

The University Pompeu Fabra (UPF, www.upf.edu/english/web) is a young but very active public university located in the city of Barcelona. It is specialised in three scientific fields: Social Sciences and Humanities, Information and Communication Technologies, and Health and Life Sciences. UPF is the promoter of the Barcelona Biomedical Research Park (PRBB, www.prbb.org).

UPF will participate in this project through the Research Unit on Biomedical Informatics (GRIB, www.imim.es/grib), which is a joint research unit of UPF and IMIM-Hospital del Mar (www.imim.es/imim_eng). GRIB, located in the PRBB, carries out fundamental research and technological developments on the application of advanced information technologies and computational methods in health and life sciences. GRIB brings together a team of over sixty scientists, as well as technical and management staff. GRIB has a wide experience in the participation and coordination of research projects funded by the European Commission. In the last years, the unit has participated in 14 European projects. The GRIB is also involved in a significant number of other research projects funded by research funding agencies. GRIB has a long tradition of collaboration with the industry in the framework of R&D projects. GRIB is involved in pre and postgraduate teaching on life sciences, and in particular in the MSc in Bioinformatics in Health Sciences (diana.imim.es/Bioinformatics).

The GRIB is currently organised in seven laboratories: Computational Genomics; Structural Bioinformatics; Computational Biophysics and Biochemistry; Chemogenomics; Computer-Assisted Drug Design; Complex Systems and Integrative Biomedical Informatics.

Key personnel

Ferran Sanz: Director of the GRIB. Full professor of Biostatistics and Biomedical Informatics at the UPF, currently Vice-rector for Scientific Policy of the University. Author of more than 80 articles published in SCI indexed journals. Mentor of 16 PhD thesis. Coordinator of several EC-funded initiatives. President of the European Federation for Medicinal Chemistry from 2003 to 2005, currently member of its Executive Committee as Past-President. Involved as invited expert in the genesis of the Innovative Medicines Initiative (www.imi-europe.org) and currently coordinator of its Spanish mirror.

Jordi Mestres: Degree in computational chemistry (1996). Head of Computational Medicinal Chemistry of Organon Research (2000-2003). In 2003, created the Chemogenomics Laboratory in the GRIB. In 2006, he was the recipient of the Hansch Award from the QSAR and Modelling Society. His current interests focus on the development of an integrated chemogenomics platform for the systematic annotation of all molecules to all targets. He is author of over 70 research publications, 4 patents among them.

Recent publications relevant to the project

- Mestres J, Martín-Couce L, Gregori-Puigjané E, Cases M, Boyer S. A Ligand-based Approach to In Silico Pharmacology: Nuclear Receptor Profiling. J Chem Inf Model 2006; 46: 2725-36.
- Bonis J, Furlong LI, Sanz F. OSIRIS: a tool for retrieving literature about sequence variants. Bioinformatics 2006; 22: 2567-9.
- Gregori-Puigjané E, Mestres J. SHED: Shannon Entropy Descriptors from Topological Feature Distributions. J Chem Inf Model 2006; 46: 1615-22.
- Fontaine F, Pastor M, Zamora I, Sanz F. Anchor-GRIND: Filling the Gap between Standard 3D QSAR and the GRid-INdependent Descriptors. J Med Chem 2005; 48: 2687-94.
- Mestres J. Structure Conservation in Cytochromes P450. Proteins 2005; 58: 596-609.

Participant 4: University of Aveiro – IEETA (UAVR)

The *Instituto de Engenharia Electrónica e Telemática de Aveiro* is one of the 17 Research Units belonging to the University. Currently with a full-time staff of 72 persons (47 PhDs), developing their activities in 4 laboratories and 3 transverse activities with other research units of the University. IEETA was involved in several EU projects in the area of health. Recently coordinator of TEAM-HOS (IST-11567) and INFOGENMED (IST-2001-39013) projects, and member of the INFOBIOMED NoE (IST2002-507585). IEETA also leads several R+D projects and technology transfer projects funded by the Portuguese Agency of Research. On-going general research and development efforts focus on: signal and image processing; information systems; computer systems, electronics and robotics; bioinformatics; tomography and epilepsy. Other areas, currently developed with an interest for the project, are: integration of clinical and genetic data in the EHR; integration of clinical information and visualization; information retrieval and data mining; web systems and technologies; digital libraries applied to health; distributed environments in healthcare. The activities within the project will be lead by the Bioinformatics group with expertise in areas such as molecular biology, chemistry, statistics, computing and information systems. Strong expertise in biomedical engineering and medical informatics with collaborations with national and international research and clinical groups.

Key personnel

José Luis Oliveira: Associate Prof., leader of the bioinformatics group at IEETA. Director of the bioinformatics unit at BIOCANT. Vice-director of the Electronics, Telecommunications and Informatics Department of UAVR. PhD on distributed systems and network management. Main research interests: in the area of computational methods for bioinformatics and biomedical informatics. Recent IST projects: InfoGenMed, Daidalos, EuroNGI (NoE), InfoBioMed (NoE). Member of several scientific committees. More than 100 papers.

Carlos Manuel Azevedo Costa: Assistant Prof., PhD in Medical Informatics. Author or co-author of more than 30 publications in the Medical Informatics area, including 1 patent. He has been deeply involved in health care projects concerning EHR, PACS, privacy and access control issues. Research interests: electronic health records, healthcare information systems, medical imaging systems and telemedicine.

António Sousa Pereira: Full Prof, leader of Information Systems and Telematics Lab of IEETA. PhD in Medical Imaging. He has been responsible in several R&D national and European projects in the area of telematics applied to health care, specially in the telemedicine domain (INFOGENMED, ITHACA, EPIC, HOSPITAL 2000, ISCAMI, MOMS, TELEMIL, GIMEC). Member of the Task Force Y2000, organized by the Portuguese Ministry of Health. Member of the Working Party of the Programme TELEMATICS - Healthcare, of the CEC DG – XIII, in FP5. Prizes: Lepetit prize (1986), Thomé Villar (1989, 1990), Marie Curie prize by the EANM.

Recent publications relevant to the project

- Costa C, Silva A, Oliveira JL. Current perspectives on PACS with a case study on Cardiology. Book chapter in Computational Intelligence in Healthcare. Elsevier. 2007. In press
- Costa C, Silva A, Oliveira JL, Ribeiro V, Ribeiro J. A demanding Web-based PACS supported by Web Services technology. In: Steven OR Horii C, Ed. Medical Imaging 2006: PACS and Imaging Informatics. Vol. 6145, 2006.
- Pinheiro M, Afreixo V, Moura G, Freitas A, Santos MA, Oliveira JL. Statistical, computational and visualization methodologies to unveil gene primary structure features. Methods of Information in Medicine 2006: 45; 163-8.
- Dias G, Oliveira JL, Vicente F, Martín-Sanchez F. Integrating Medical and Genomic Data: a Successful Example for Rare Diseases. XX International Congress of the European Federation for Medical Informatics (MIE'2006), Maastricht, Netherlands, 2006.
- Oliveira I, Oliveira JL, Sanchez JP, López-Alonso V, Martin-Sanchez F, Maojo V, Pereira AS. Grid requirements for the integration of biomedical information resources for health applications. Methods of Information in Medicine 2005: 44; 161-7.

Participant 5: IRCCS Centro Neurolesi "Bonino-Pulejo" (NEUROLESI)

NEUROLESI is a research organization that is directly funded from Italian Health Ministry to carry out clinical research and care in the neurological field. Part of this centre is our laboratory of pharmacovigilance and pharmacoepidemiology, the activity of which is targeted to monitor and to evaluate drug utilization and safety, in particular (but not exclusively), neuropsychiatry drugs. Our lab represents the Sicilian Regional Pharmacovigilance centre and collects all spontaneous ADR reports from Sicily and provides any reporter with individual and personalized feedback containing a qualified comment on ADRs described and a detailed causality assessment. Since 1996, is included in the GIF (interregional group of pharmacovigilance). GIF is based on spontaneous ADR reporting data coming from 8 Italian Regions that have joined progressively the project, to maintain a pooled ADR database. These regions cover about 60% of Italian general population (more than 35M of inhabitants) and account for almost 75% of the national spontaneous ADR reports. Our group participates in exploring such pharmacovigilance database to detect signals arising from collected ADR reports. Moreover, our lab is an Information Center about Drugs on behalf of the Italian Society of Pharmacology and scientifically manages www.farmacovigilanza.org, an Italian independent website that provides health professionals with highly qualified information about drug safety, derived from scientific literature and regulatory agencies.

Key personnel

Achille Patrizio Caputi: graduated in Medicine (University of Naples, 1970). Since 1980, full professor of Pharmacology, School of Medicine, Univ. of Messina. Chief of Depart. of Clinical and Experimental Medicine and Pharmacology of the University and Incoming President of the Italian Society of Pharmacology. Member of Directory Board of several scientific societies. Scientific Manager of www.farmacovigilanza.org. Member of the Pharmacovigilance Committee of the Italian Ministry of Public Health.

Edoardo Spina: graduated in Medicine (Univ. of Messina 1981). Specialist in Neurology and in Psychiatry (1987). PhD at the Depart. of Clinical Pharmacology, Huddinge Univ. Hospital, Karolinska Institute, Stockholm. Full professor of Pharmacology at the Depart. of Clinical and Experimental Medicine and Pharmacology, Univ. of Messina. Author of 150 papers and 180 abstracts. Member of scientific societies and editorial board of a number of scientific journals.

Gianluca Trifirò: graduated in Medicine (Univ. of Messina 2002). Specialist in Clinical Pharmacology (2006). He is doing a PhD about safety of neuropsychiatry medications at the Department of Medical Informatics of Erasmus Medical Center (Rotterdam). Author of papers about pharmacovigilance issues, referee for scientific journals and member of several scientific societies addressing drug safety issues. Responsible of "Drug safety in Clinical Trials" at www.farmacovigilanza.org.

Recent publications relevant to the project

- Trifiro G, Calogero G, Ippolito FM, Cosentino M, Giuliani R, Conforti A, Venegoni M, Mazzaglia G, Caputi AP. Adverse drug events in emergency department population: a prospective Italian study. Pharmacoepidemiol Drug Saf 2005; 14: 333-40.
- Polimeni G, Salvo F, Cutroneo P, Morreale I, Caputi AP. Adverse reactions induced by NSAIDs and antibacterials: analysis of spontaneous reports from the Sicilian regional database. Drug Saf 2006; 29: 449-59.
- Salvo F, Polimeni G, Moretti U, Conforti A, Leone R, Leoni O, Motola D, Dusi G and Caputi AP. Adverse drug reactions related to amoxicillin alone and in association with 1 clavulanic acid: data from spontaneous reporting in Italy. J Antimicrob Chemother. In press.
- Trifiro G, Corrao S, Alacqua M, Moretti S, Tari M, Caputi AP, Arcoraci V; UVEC Group. Interaction risk with proton pump inhibitors in general practice: significant disagreement between different drug-related information sources. Br J Clin Pharmacol 2006; 62: 582-90.
- Trifiro G, Verhamme KM, Ziere G, Caputi AP, Ch Stricker BH, Sturkenboom MC. All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. Pharmacoepidemiol Drug Saf. 2006 Oct 12; [Epub ahead of print]

Participant 6: Université Victor-Segalen Bordeaux II (UB2)

Université Victor-Segalen Bordeaux II is the University of Sciences of Health, Life and Man at Bordeaux (France) (http://www.u-bordeaux2.fr), with 18000 students, 2000 faculty and researchers. It is linked to the Bordeaux University Hospital (3800 beds). Among its many research teams and groups, it includes a large department of pharmacology (100 persons) and an Institute of Public Health (ISPED).

The Department of Pharmacology, which leads the local contribution to the project, includes the Regional Pharmacovigilance Centre and a Pharmacoepidemiology unit. This unit (50 persons) conducts large field studies of drug utilization, safety and performance. The Department of Pharmacology is part of the research network INSERM U657: pharmacoepidemiology and real-life impact of drugs research network (with teams in Bordeaux, Rouen (Pr J. Benichou), Paris (Pr L. Abenhaim, Pr D. Guillemot)). The head of this research network is Professor Bernard Bégaud, President of the University. Among the research themes of this network, one is dedicated to automated alert generation in Pharmacovigilance using disproportionality analyses. Members of the team have in addition in the past been associated with adverse reaction terminology efforts, leading to Meddra.

Key personnel

Prof. Bernard Bégaud: MD, PhD, director of the INSERM U657 Research Network, President of Université Bordeaux 2.

Prof. N. Moore: MD, PhD, head of the department of Pharmacology, Bordeaux, President of the International Society of Pharmacovigilance, vice-chairman of the European Association of Clinical Pharmacology and Therapeutics, board member and fellow of the International Society of Pharmacoepidemiology, who will be the team leader. This team also includes **Prof. Annie Fourrier**: PharmD, PhD, associate professor, team coordinator, and **Antoine Pariente**: MD and PhD student, assistant, and support persons as needed (including database managers, IT experts, statisticians from the pharmacoepidemiology Unit (www.pharmacoepi.eu)), as well as Pharmacovigilance experts **Francoise Haramburu** MD (FH) and **Ghada Miremont** MD (GMS) from the Regional Pharmacovigilance Centre.

Prof. M. Fieschi: MD, PhD, head of LERTIM (Marseilles), who will coordinate with **M. Joubert,** PhD, Dr **F. Thiessard** MD, PhD (ISPED) and Dr **P. Avillach**, MD, PhD student, the terminology part of the Bordeaux Team contribution.

Recent publications relevant to the project

- Pariente A, Gregoire F, Rourrier-Réglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf 2007. In press.
- Moore N, Thiessard F, Begaud B. The history of disproportionality measures (reporting odds ratio, proportional reporting rates) in spontaneous reporting of adverse drug reactions. Pharmacoepidemiol Drug Saf 2005; 14: 285-6.
- Roux E, Thiessard F, Fourrier A, Begaud B, Tubert-Bitter P. Evaluation of statistical association measures for the automatic signal generation in pharmacovigilance. IEEE Trans Inf Technol Biomed 2005; 9: 518-27.
- Moore N, Hall G, Sturkenboom M, Mann R, Lagnaoui R, Begaud B. Biases affecting the proportional reporting ratio (PRR) in spontaneous reports pharmacovigilance databases: the example of sertindole. Pharmacoepidemiol Drug Saf 2003; 12: 271-81.
- Moore N, Kreft-Jais C, Haramburu F, Noblet C, Andrejak M, Ollagnier M, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. Br J Clin Pharmacol 1997; 44: 513-8.
- Gaudinat A, Ruch P, Joubert M, Uziel P, Strauss A, Thonnet M, et al. Health search engine with e-document analysis for reliable search results. Int J Med Inform 2006; 75: 73-85.
- Joubert M, Peretti AL, Gouvernet J, Fieschi M. Refinement of an automatic method for indexing medical literature - a preliminary study. Stud Health Technol Inform 2005; 116: 683-8.

Participant 7: London School of Hygiene & Tropical Medicine (LSHTM)

The **London School of Hygiene & Tropical Medicine** is Britain's national school of public health. It is an internationally recognized centre of excellence in epidemiology and biostatistics, and one of the highest-rated research institutions in the UK.

LSHTM will collaborate with academics from Imperial College London. The research group has considerable experience in research involving primary care and prescribing data, pharmaco-epidemiology, and computational methods for analysing large, complex datasets. Collaboration between the groups has already begun, using preliminary data supplied by MediPlus and THIN, and bringing together expertise in epidemiology, computing and statistics. We have also explored the use of primary care databases for case ascertainment of adverse drug reactions as part of the EUDRAGENE collaboration. We have already written to compile tables, correct errors, and generate summary statistics for further analysis. We have tested the ability to detect signals of two well-recognized drug-adverse event combinations in a case-crossover design: statins with myopathy; and tendon rupture with fluoroquinolones. Furthermore MM and JW have experience in a number of epidemiological studies involving complex data interpretation and evidence synthesis. LSHTM will specifically contribute to terminology mapping; data mining; literature and database mining and prospective validation. Computing and data mining support will be provided by Imperial College.

Key personnel

Mariam Molokhia is Clinical Lecturer in Epidemiology at LSHTM. She is the co-coordinator of the EUDRAGENE project (European case-control collaboration to study genetic susceptibility to adverse drug reactions) and has experience conducting and developing methodologies for a number of epidemiological studies of complex traits. She has received funding from the Department of Health (NCCRCD) for research into adverse drug reactions using primary care data.

John Whittaker is Professor of Genetic Epidemiology and Statistics at LSHTM and has considerable expertise in statistical methodology, particularly the application of Bayesian methods to complex biomedical data. He will provide advice on statistical methodology for signal detection and dealing with multiple testing issues.

Recent publications relevant to the project

- Lucena MI, Molokhia M, Cueto R, Serrano Carballo A, Carvajal A, Andrade RJ. Genetic and Molecular factors in drug-induced liver injury: a review. Current Drug Safety. In press 2007.
- Molokhia M, McKeigue P. EUDRAGENE: European collaboration to establish a case-control DNA collection for studying the genetic basis of adverse drug reactions. Pharmacogenomics 2006; 7: 633-8.
- Baksh MF, Balding DJ, Vyse TJ, Whittaker JC. Family-based association analysis with ordered categorical phenotypes, covariates and interactions. Genet Epidemiol 2007; 31: 1-8.
- Hubner N, Wallace CA, Zimdahl H, Petretto E, Schulz H, Maciver F, Mueller M, Hummel O, Monti J, Zidek V, Musilova A, Kren V, Causton H, Game L, Born G, Schmidt S, MŸller A, Cook SA, Kurtz TW, Whittaker J, Pravenec M, Aitman TJ. Integrated transcriptional profiling and linkage analysis for identification of genes underlying disease. Nat Genet 2005; 37: 243-53.
- Verzilli CJ, Stallard N, Whittaker JC. Bayesian modelling of multivariate quantitative traits using seemingly unrelated regressions. Genet Epidemiol 2005; 28, 313-25.

Participant 8: Aarhus University Hospital / Aarhus Sygehus (AUH-AS)

The Aarhus University Hospital will participate in the project through their Department of Clinical Epidemiology (DCE), which was established in 2000 in collaboration between two Danish counties and Aarhus University. The department is part of the Clinical Institute at Aarhus University and has two research sections in Aarhus and Aalborg. DCE deals with a broad spectrum of clinical epidemiological topics and has approximately 50 employees. It is a department where clinical experience, biological knowledge, advanced biostatistics, lab research, medical informatics and computer technology are integrated. The department is continuously looking to optimize diagnostics and treatment of diseases and to prevent recurrence and complications through research and education.

Key personnel

Henrik Toft Sørensen: Head of Department of Clinical Epidemiology. DMSc, Clinical Epidemiology (1996), PhD, Clinical Epidemiology (1994) and MD (1983) at Aarhus University, Aarhus, Denmark. Adjunct professor at Boston University (2004) and Adjunct professor, Vanderbilt University, USA (2001). Professor of Clinical Epidemiology at the University of Aarhus, Denmark (2000). He was also a visiting professor at Dartmouth Medical School, USA (1999) and Associate professor of Epidemiology and Internal Medicine, University of Aarhus, DK (1994-2000). From 1991 to 1992 he was an Associate professor of Internal Medicine, University of Aarhus, Denmark

More than DKK 25 Million in research grants over the last 10 years for clinical pharmacoepidemiology and co-investigator on 4 projects supported by National Institutes of Health, USA. Total number of publications in PubMed: 480. Total number of citations in Scopus: 4766. H-index: 34 over the last 10 years

Lars Pedersen: Associate professor, chief statistician. MSc. in Statistics, Department of Theoretical Statistics, University of Aarhus (1999). Associate Professor, Faculty of Health Science, University of Aarhus (2003); Manager of Statistics, Department of Clinical Epidemiology, University of Aarhus (2000); Junior Statistician, Danish Epidemiology Science Center, University of Aarhus (1998-1999). Co-investigator on grants amounting to DKK 5.1 million. Total number of publications in PubMed: 65.

Recent publications relevant to the project

- Christensen S, Riis A, Nørgaard M, Thomsen RW, Sørensen HT. Introduction of newer selective cyclo-oxygenase-2 inhibitors and rates of hospitalization with bleeding and perforated peptic ulcer. Aliment Pharmacol Ther 2007; 25: 907-12.
- Langagergaard V, Pedersen L, Gislum M, Nørgård B, Sørensen HT. Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: A Danish nationwide cohort study. Aliment Pharmacol Ther 2007; 25: 73-81.
- Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sørensen HT, Væth M, Obel N. Survival of Persons with and without HIV-infection in Denmark 1995-2005. Ann Intern Med 2007; 146: 87-95.
- Dalton SO, Johansen C, Poulsen AH, Nørgaard M, Sørensen HT, McLaughlin JK, Mortensen PB, Friis S. Cancer risk among users of neuroleptic medication: a population-based cohort study. Br J Cancer 2006; 95: 934-9.
- Lohse N, Obel N, Kronborg G, Jørgensen LB, Pedersen C, Larsen CS, Kvinesdal B, Sørensen HT, Gerstoft J. Declining prevalence of HIV-infected individuals at risk of transmitting drug-resistant HIV in Denmark during 1997–2004. Antivir Ther 2006; 11: 591-600.

Participant 9: AstraZeneca AB (AZ)

The activities of the Research and Development group at AstraZeneca Mölndal focus primarily on the computational and informatics aspects of the interaction of drug molecules with biological systems. The methods used are quite varied: from quantum mechanical calculations to searching and knowledge development from chemical and biological databases. Research activities are involved primarily with the information around the safety of new drug candidates. In this role they accumulate patient data as it relates to clinical safety, organise it into databases and mine those databases for trends that will help identify patients at risk or chemical subtypes in drug molecules that should be avoided. Their specialty is in prediction of biotransformation of drugs and in human drug-drug interactions. The group maintains several large research collaborations in the areas of data mining and computational chemistry. Expected role in the network is to represent, in part, the views of large pharmaceutical industry in setting goals for the project and to contribute to evaluations in an industrial setting of the project output.

As one of the top five pharmaceutical companies in the world, AstraZeneca is a member of 'big pharma' with one of the largest drug discovery research staffs in the world, distributed over 9 major research sites in Europe, North America and Asia. AstraZeneca is also a 'complete' pharmaceutical organisation, discovering, developing and marketing therapeutics.

Most scientists within the organisation are directly involved in the day-to-day operation of drug discovery and development projects and thus there exists an atmosphere of enthusiastic innovation tempered by the realities of drug discovery. Thus as a participant in this Consortium, we are expecting to act as a 'test-bed' for both new ideas and new products. We also anticipate contributing our perspectives consistently throughout this period in order to bring a realistic perspective to the innovations that are sure to be a product of this project.

Our group is responsible for informatics tools that aid in drug discovery project decision-making. These tools range from predictive models of biological effect to informatics tools for exploring large and diverse data sources. One area that has become a priority within AstraZeneca (and most probably within most other organisations) is cross-disciplinary data sharing and integration – particularly when it comes to extrapolating effects from models to humans. Thus this project and the products thereof are of keen interest to our organisation.

Key personnel

Scott Boyer, Ph.D. Principal Scientist, Safety Assessment. Head of Computational Safety and Informatics department. Specialties include predictive models of biological endpoints, data mining, chemical genetics and human adverse event modelling.

Recent publications relevant to the project

- Gavaghan CL, Arnby CH, Blomberg N, Strandlund G, Boyer S. Development, interpretation and temporal evaluation of a global QSAR of hERG electrophysiology screening data. J Comput Aided Mol Des 2007; 21: 189-206.
- Boyer S, Arnby CH, Carlsson L, Smith J, Stein V, Glen RC. Reaction site mapping of xenobiotic biotransformations. J Chem Inf Model 2007; 47: 583-90.
- Glem RC, Bender A, Arnby CH, Carlsson L, Boyer S, Smith J. Circular fingerprints: flexible molecular descriptors with applications from physical chemistry to ADME. IDrugs 2006; 9: 199-204.
- Cases M, Garcia-Serna R, Hettne K, Weeber M, van der Lei J, Boyer S, Mestres J. Chemical and biological profiling of an annotated compound library directed to the nuclear receptor family. Curr Top Med Chem 2005; 5: 763-72.
- Apic G, Ignjatovic T, Boyer S, Russell RB. Illuminating drug discovery with biological pathways. FEBS Lett 2005; 579: 1872-7.

Participant 10: University of Nottingham (UNOTT)
Nottingham University is a research led university which is ranked in the top 10 universities in the UK and within the top 75 in the world. It has an extensive portfolio of medical research spanning several decades and is well known for expertise in primary care informatics. It has been a partner in a number of EU funded projects relating to the use of electronic medical records and prescribing (Pharmdis and eHID). It has two Nobel prize winners in the last four years.

Key personnel
Julia Hippisley-Cox: Professor of Clinical Epidemiology & General Practice at the Division of Primary Care, School of Community Health Sciences, University of Nottingham. She is also a clinical General Practitioner. FRCGP (2006), MD (1998), MRCP (1994), MbChB (1989). She is co-director and cofounder of QRESEARCH which is an academic organisation specialising in research using primary care electronic data. QRESEARCH is a not-for-profit partnership between Nottingham University and EMIS – the leading supplier of IT to General practice covering 60% of UK. The main QRESEARCH database is the largest patient level primary care research database in the world (http://www.qresearch.org) It is ideally suited for modelling drug safety because of its size, data quality, timeliness and the availability of data on confounders (such as socioeconomic status). Most recently it has been linked to mortality data. QFLU is a near real time surveillance system for infectious diseases covering a population of 24 million patients set up to alert to and manage a flu pandemic. Research interest: risk prediction modelling of common diseases in primary care, assessment of risks and benefits of new and commonly used medicines. Her paper on safety of traditional NSAIDs and Cox (BMJ 2005) was ranked the top paper in the BMJ for 2005.
Carol Anne Charlotte Coupland: Since 2000 she is an Associate professor in Medical Statistics at the Division of Primary Care, School of Community Health Sciences, University of Nottingham. PhD, University of Nottingham (2005), CStat, Royal Statistical Society (2000), M.Sc. in Biometry. University of Reading (1986) and BSc. (Honours) in Mathematics: First Class. University of Exeter (1985).
Yana Vinogradova: research statistician working mostly on projects based on QRESEARCH database. She joined the University of Nottingham in 2005 and has worked extensively in epidemiological studies. She is a mathematician by training (graduated in 1984, Moscow State University) with a strong interest in epidemiology. Her research involves the use of mathematical models and statistical methods to improve understanding of dynamics and incidence of diseases. She is currently involved in development and application of mathematical models for CVD risk assessment and in studying effects of statin use on general population.

Recent publications relevant to the project
- Hippisley-Cox J, Coupland CAC. Effect of statins on the mortality of patients with ischaemic heart disease: population based cohort study with nested case-control analysis. Heart 2006; 92: 752-8.
- Hippisley-Cox J, Coupland CAC. Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis. BMJ 2005; 330: 1059-63.
- Hippisley-Cox J, Coupland CAC. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005; 330: 1366.
- Hippisley-Cox J, Coupland CAC, Logan R. Risk of adverse gastro-intestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflamatory drugs: population based nested case-control analysis. BMJ 2005; 331: 1310-1316.
- Hippisley-Cox J, Hammersley V, Pringle M, Coupland C, Crown N, Wright L. Methodology for assessing the usefulness of general practice databases for research in one research network. Health Informatics Journal 2004; 10: 91-109.

Participant 11: Universitá degli Studi di Milano-Bicocca (UNIMIB)

Department of Statistics is active since January 1999 at University of Milan-Bicocca, Milan, Italy. The goals that motivated the birth of the Department, in a scientific area not yet sufficiently represented in the Universities of Milan, are promoting and co-ordinating the research in the fields of theoretical and applied statistics, stimulating the didactic updating, and contributing to spread the statistical culture in universities and in institutions. In 2007, the Department concurs in the didactic activity of two undergraduate degree courses (3 years), two graduate degree courses (2 years) and one Master (6 months). The Department offers also a doctoral program in Statistics in collaboration with the Universities of Milan (Faculty of Political Sciences), Turin (Faculties of Political Sciences and of Economics), and the Catholic University of Milan (2nd Faculty of Economics). The Department adheres to two research centres: CRISP (interuniversity research centre for the public utility services) and SET (centre for advanced studies in theoretical economics). A documentation centre for economic, social-demographic and health statistics is actually active at the Department, and a database for accessing national (Istat in first place) and international (Eurostat, U.N., World Bank) statistics is about to be implemented.

One research Unit of the Department is the Unit of Biostatistics and Epidemiology, which is involved in collaborative epidemiological and statistical research projects within and external to the department. It also provides statistical support to the department's staff and students, and its components are present in almost all Faculty's teaching programs. The principal aims of this Unit are to design studies and to analyze data using statistical methods that are suitable for the biomedical and epidemiological needs of specific projects; to develop new methods where needed by consulting with researchers of the other units; to provide lectures and seminars on statistical medical issues for researchers and statisticians of the Department or for external researchers.

Key personnel

Giovanni Corrao, Full Professor of Medical Statistics, Coordinator of graduate degree course “Biostatistical and experimental statistics”, Head of the Unit of Biostatistics and Epidemiology, Department of Statistics, University of Milano-Bicocca. At present, his principal research interest mainly concerns the planning of epidemiological studies to estimate clinical and economic implications of pharmacological treatment on some chronic conditions, such as hypertension, type 2 diabetes, hyperlipidemia, and osteoporosis.

Antonella Zambon, Research fellow, afferent to the Unit of Biostatistics and Epidemiology, Department of Statistics, Univ. of Milano-Bicocca. Her research is focused on the comparison of emergent and classical observational designs in the pharmacoepidemiology framework.

Federica Nicotra, PhD student of the Department of Statistics, Unit of Biostatistics and Epidemiology, University of Milano-Bicocca. She actually focuses on the review in detail of the definition, the indicators and the modelling of drug compliance in pharmacoepidemiology.

Recent publications relevant to the project

- Mancia G, Bombelli M, Corrao G, *et al.* Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. Hypertension 2007; 49: 40-7.
- Bagnardi V, Botteri E, Corrao G. Empirical-Bayes adjustment improved conventional estimates in postmarketing drug-safety studies. J Clin Epidemiol 2006; 59: 1162-8.
- Corrao G, Zambon A, Bertù L, Mauri A, Paleari V, Rossi C, Venegoni M. Evidence of tendinitis provoked by fluoroquinolone treatment: a case-control study. Drug Saf 2006; 29: 889-96.
- Corrao G, Zambon A, *et al.* Exploring the effect of transient exposure on the risk of acute events by means of time-window designs: an application to fluoroquinolone antibacterials and arrhythmia. Pharmacoepidemiol Drug Saf 2006; 15: 31-7.
- Corrao G, Zambon A, *et al.* Short-acting inhaled beta-2-agonists increased the mortality from chronic obstructive pulmonary disease in observational designs. J Clin Epidemiol 2005; 58: 92-7.

Participant 12: Agenzia Regionale di Sanità della Toscana (ARS)

ARS is a public scientific structure aimed to support the Regional Government for its programming activities through the production of scientific data. The main activities of this organization are focused on epidemiological research and quality evaluation of health services. Research is mainly developed throughout the integrated use of administrative data on health services and population health status. The regional database from Tuscany is an integrated database containing information for both demographic and health records relative to around 3.5 million residents in the *Regione Toscana* (demographic information, hospital discharges, cause-specific mortality, and drug claims). The data bases are linked through a personal unique identifier (fiscal code). Computerized procedures to test the validity and completeness of linked data have been performed. ARS is collaborating with the Ministry of Health and with national and international scientific institutions on projects regarding appropriateness of drugs prescription, adverse effects of drugs and of drug combination, outcomes of treatment and risk-benefit profiles of the medications. Furthermore, ARS is involved in epidemiological projects on specific populations at risk, such as elderly residents and disability risk, newborn underweight infants and disability/death risk, hospitalization and disease risk in migrants from underdeveloped countries. These projects are conducted in cooperation with national and international research groups.

Key personnel

Dr Eva Buiatti: graduate in Medicine at the University of Florence (1968). Specialist in Toxicology, in 1971, in Public Health in 1976 and Oncology in 1986. She is currently the Head of the Epidemiology Unit of the Regional Health Agency of Tuscany and the Scientific Coordinator of the Regional Health Agency of Tuscany. Among the fields of interest: the use of claims data relevant to public health based on mortality, hospitalization, drugs, and different pathologies (AIDS, infective diseases registries); validation and integrated use of current data also for producing "Reports on state of public health". She is member of several scientific societies and is referee of a number of scientific journals. Author of around 140 papers in peer reviewed journals, in many of which the use of routine data is involved.

Recent publications relevant to the project

- Monami M, Balzi D, Lamanna C, Barchielli A, Masotti G, Buiatti E, Marchionni N, Mannucci E. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. Diabetes Metab Res Rev 2007 Mar 23; [Epub ahead of print]
- Plummer M, Vivas J, Lopez G, Bravo JC, Peraza S, Carillo E, Cano E, Castro D, Andrade O, Sanchez V, Garcia R, Buiatti E, Aebischer C, Franceschi S, Oliver W, Munoz N. Chemoprevention of precancerous gastric lesions with antioxidant vitamin supplementation: a randomized trial in a high-risk population. J Natl Cancer Inst 2007; 99: 137-46.
- Balzi D, Barchielli A, Buiatti E, Franceschini C, Lavecchia R, Monami M, Santoro GM, Carrabba N, Margheri M, Olivotto I, Gensini GF, Marchionni N; AMI-Florence Working Group. Effect of comorbidity on coronary reperfusion strategy and long-term mortality after acute myocardial infarction. Am Heart J 2006; 151:1094-100.
- Bucchi L, Barchielli A, Ravaioli A, Federico M, De Lisi V, Ferretti S, Paci E, Vettorazzi M, Patriarca S, Frigerio A, Buiatti E; SCREENREG Working Group. Screen-detected vs clinical breast cancer: the advantage in the relative risk of lymph node metastases decreases with increasing tumour size. Br J Cancer 2005; 92: 156-61.
- Buiatti E, Barchielli A, Marchionni N, Balzi D, Carrabba N, Valente S, Olivotto I, Landini C, Filice M, Torri M, Regoli G, M Santoro G. Determinants of treatment strategies and survival in acute myocardial infarction: a population-based study in the Florence district, Italy. Results of the acute myocardial infarction Florence registry (AMI-Florence) Eur Heart J 2003; 24:1195-203.

Participant 13: PHARMO COOPERATIE UA (PHARMO)

The PHARMO Cooperatie is an expert centre for drug evaluation dedicated to perform and facilitate outcomes research, in particular to contribute to a better understanding of drug use, the effectiveness of drugs as well as the safety of drug as used in daily practice. The centre of the Institute is a large multi-event observational data base, including day-by-day patient centric organized data on in- and outpatient drug exposure, hospitalizations, accidents, clinical laboratory findings, function test, cancer registries and more (www.PHARMO.com).

Key personnel

Ron MC Herings, Ph.D., FISPE, Associate Professor Erasmus MC Rotterdam. Dr. Herings is founder of the PHARMO Medical Record Linkage System and the director of The PHARMO Institute. He has broad experience in pharmacoepidemiology, in particular probabilistic record linkage method for which he as awarded the Dutch Innovation price in medical informatics in 1997. He is member of the editorial board of several journals, lectured pharmacoepidemiological and biostatistical principles for more than 10 years at the department of Pharmacoepidemiology, Utrecht University.

He authored over hundred publications related to different topics in pharmacoepidemiology and outcomes research.

Joëlle A. Erkens, PharmD, Ph.D. Dr. Erkens is Manager Business Development & Global Accounts at The PHARMO Institute and will be responsible for overseeing all aspects of the study and collaborative efforts between PHARMO and the other institutions involved.

Her expertise in drug pharmaco-epidemiology, mainly focused on effectiveness and safety research of drugs in daily practice is a key component to the project.

Fernie J.A. Penning-van Beest, Ph.D. Dr. Penning-van Beest is Research Quality Manager at the PHARMO Institute and will be responsible for overseeing all aspects of the study.

Her expertise in drug pharmaco-epidemiology mainly focused on effectiveness and safety research of drugs in daily practice is a key component to the project.

Recent publications relevant to the project

- Penning-van Beest FJ, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJP, Herings RMC. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. Eur Heart J 2007; 154-9.
- Gibbons RD, Hendricks Brown C, Hur K, Marcus SM, Bhaumik DK, Erkens JA, Herings RM, Man JJ. Early evidence on the effects of regulators'suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007; 1356-63.
- Breekveldt-Postma NS, Koerselman j, et al. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. Respir Med 2007.
- Penning-van Beest FJ, Erkens JA, Olson M, Herings RM. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporos Int 2007 Sep 14.
- Goettsch WG , de Jong RB, etal. Developments of the incidence of osteoporosis in The Netherlands: a PHARMO study. Pharmacoepidemiol Drug Saf 2007; **16**(2): 166-72.

Participant 14: Società Servizi Telematici SRL (PEDIANET)

The possibility of accessing data from the daily activities of paediatric general practitioners and family paediatricians is a unique resource, both for studying individual diseases, as well the interactions between different areas of health care and population health. In 1998 a network (Pedianet) has been established in Italy to collect epidemiological information for clinical research from family paediatricians. This system is based on the transmission of specific data (determined by individual studies) from computerised clinical files, which the paediatricians in the network fill out during their daily professional activities. Informed consent is required from the parents. Such data is collected anonymously by a central server in Padua, where it is validated and elaborated. The database is owned by a SME called Società Servizi Telematici.

Pedianet is an independent network. The coordination of the projects and data analysis are carried out by a scientific committee that include internationally well known paediatricians, epidemiologists and researchers. Approximately 300 paediatricians throughout the country have taken part in Pedianet projects. Over 20 clinical epidemiological studies on major paediatric diseases or pharmacovigilance have been carried out or were ongoing up to June 2007. These studies have resulted in over 50 publications and presentations at conferences. Studies carried out to-date have been financed by public bodies (EC, Istituto Superiore di Sanità, AIFA, Consiglio Nazionale delle Ricerche, Regione Veneto, Aziende Socio Sanitarie, Istituto Zooprofilattico delle Venezie etc) or private groups such as pharmaceutical companies or international research groups.

In January 2007, a new law came into force in Europe and for registration of new drugs it is mandatory to present a Paediatric Investigation Plan to EMEA. There are also a number of incentives for companies obtaining a paediatric licence for drugs which are already on the market, both under patent and "off patent". In this new context the role of Pedianet, not just as a database (especially for pharmacovigilance studies), but as an organised structure in which different competencies converge, is essential. This is confirmed by the presence and participation of Pedianet in important European projects, such as TEDDY (www.teddyoung.org) an EU funded NoE, as well as by the increasing interest European institutions, research groups and pharmaceutical companies are showing to collaborate with Pedianet.

Key personnel

Carlo Giaquinto MD, Paediatrician working at the Dept. of Pediatrics of Padova. Honorary Senior Lecturer at the Dept. of Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College, London. Head of the Paediatric European network Treatment AIDS (PENTA) project funded from the EC since 1992. Scientific coordinator of Task Force Drug Development in Young (TEDDY), EU funded NoE. Scientific coordinator of Pedianet. Author of more than 180 scientific publications in peered review journal.

Luigi Cantarutti MD, Family paediatrician, chairman of the Pedianet Steering Committee, President of the Società Servizi Telematici – Pedianet. Principal investigator of several clinical-epidemiological studies and author of about 40 scientific publications in international journal.

Recent publications relevant to the project

- Nicolosi A, Sturkenboom M, Mannino S, Arpinelli F, Cantarutti L, Giaquinto C. The incidence of varicella: correction of a common error. Epidemiology 2003; 14: 99-102.
- Sturkenboom MCJM, Nicolosi A, Cantarutti L, Mannino S, Picelli G, Scamarcia A, Giaquinto C, for the NSAIDs Paediatric Research Group. Incidence of mucocutaneous reactions in children treated with niflumic acid, other non steroidal anti-inflammatory drugs and analgesics. Pediatrics 2005; 116: 26-33.
- Giaquinto C, Van Damme P, Huet F, et al. Clinical Consequences of Rotavirus Acute Gastroenteritis in Europe, 2004-2005: The REVEAL Study. The Journal of Infectious Disease 2007; 195:S26-35.
- Giaquinto C, Van Damme P, Huet F, et al. Costs of Community-Acquired Pediatric Rotavirus Gastroenteritis in 7 European Countries: The REVEAL Study. The Journal of Infectious Disease 2007; 195:S36-44.
- Giaquinto C, Callegaro S, Andreola B, Bernuzzi M, Cantarutti L, et al. Costs of community-acquired paediatric rotavirus gastroenteritis in Italy. Pharmacoeconimics 2007; 9: 103-11.

Participant 15: University of Santiago de Compostela (USC)

The University of Santiago de Compostela (USC) has a long history as an academic institution, which dates back to the 16th century. In terms of human resources, the university has more than 2,000 professional and research staff and over 30,000 students. The USC participates in the various public calls for RTD projects, at both national and international levels. Several research groups have worked actively in more than 100 projects under the IV, V and VI European Union RTD Framework Programme.

The BioFarma group is one of the leading public research groups in the field of drug discovery in Spain. The expertise of the team lies in the definition and validation of new targets and in the design and development of candidate drugs up to the preclinical development supported by public funding, twenty seven grants on drug discovery in the last five years from European Union and Spanish and Galician Governments. In this period the group signed twenty contracts with Biotech and Pharmaceutical Companies. Biofarma has promoted the constitution of a drug information system company under a European public initiative, is a member of the Pharmacogenomics Network, and runs the USEF drug screening platform (http://imaisd.usc.es/riaidt/usef/actividadesfarmacoloxicasg.asp). USEF is integrated within the CENIT Genius Pharma AIE Project granted by the Spanish Ministry of Industry which consolidates it as a leading drug screening platform. USEF uses a combination of High Throughput Screening (HTS) and high yield molecular profiling to determine the pharmacological/biological activity of compounds. The USEF has a modern, well-equipped laboratory available for assessment of the pharmacological activity of molecules, in targets as well as antitargets. More than 100.000 compounds were assayed in the last four years.

Key personnel

Mabel Loza, Ph.D. Associate Professor of Pharmacology at the University of Santiago de Compostela (USC). Coordinator of the BioFarma research group and the USEF platform at the USC. Author of more than seventeen research publications, six patents among then. Supervisor of eleven PhD thesis. Partner of six EC-funded initiatives.

Recent publications relevant to the project

- Dezi C, Brea J, Alvarado M, Raviña E, Masaguer C, Loza MI, Sanz F, Pastor M. Multi-structure 3D-QSAR studies on a series of conformationally constrained butyrophenones docked into a new homology model of the 5-HT2A receptor. Journal of Medicinal Chemistry 2007. 12;50(14):3242-55.
- Domínguez E, Loza MI, Padín F, Gesteira A, Paz E, Páramo M, Brenlla J, Pumar E, Iglesias F, Cibeira A, Castro M, Caruncho H, Carracedo A, Costas J. Extensive linkage disequilibrium mapping at HTR2A and DRD3 for schizophrenia susceptibility genes in the Galician population. Schizophrenia Research 2007;90(1-3):123-9.
- Brea J, Castro M, Loza MI, Masaguer CF, Ravina E, Dezi C, Pastor M, Sanz F, Cabrero-Castel A, Galan-Rodriguez B, Fernandez-Espejo E, Maldonado R, Robledo P. QF2004B, a potential antipsychotic butyrophenone derivative with similar pharmacological properties to clozapine. Neuropharmacology 2006;51(2):251-62.
- Padín JF, Rodríguez MA, Domínguez E, Dopeso-Reyes IG; Buceta M; Cano E; Sotelo E, Brea J, Caruncho HJ; Cadavid MI, Castro MA; Loza MI. Parallel regulation by olanzapine of the patterns of expression of 5-ht2a and d3 receptors in rat central nervous system and blood cells. Neuropharmacology 2006;51(4):923-32.
- Carotti A, Cadavid MI, Centeno NB, Esteve C, Loza MI, Martinez A, Nieto R, Raviña E, Sanz E, Segarra V, Sotelo E, Stefanachi A, Vidal B. Design, synthesis and structure-activity relationships at human A2B adenosine receptor of 1-,3-,8-and 9-substituted-9-deazaxanthines. Journal of Medcinal Chemestry 2006;49(1):282-99.

B 2.3 Consortium as a whole

At the onset of this project, a number of areas of expertise were identified that were required to be assembled together in a interdisciplinary team, in order to achieve the objective of developing a system for an earlier detection of adverse drug events. The ALERT Consortium has been carefully selected to encompass a group of organisations characterised by their scientific soundness (see section 2.2 above), proven track record, capability to effectively cooperate (arising from experience in previous projects in several cases), and enthusiasm towards the ultimate objectives of the project.

The first set of participants involves those parties that are currently using electronic healthcare records to study a diversity of issues in medicine. In recent years, the number of publications that use data obtained through the exploitation of electronic patient records in day-to-day care has exploded. In international conferences on pharmaco-epidemiology, for example, the majority of papers presented are based on data from European databases that stem from the use of electronic healthcare records. In total, eight European databases are participating in this project with, in total, records of more than 30,000,000 patients. These partners (EMC, PEDIANET, PHARMO, AUS-AH, UNOTT, UNIMIB, ARS and subcontractor SIMG) have experience in dealing with ethical and legal issues surrounding the use of healthcare records for research, and collectively can boast on an impressive collection of scientific papers. In this project, their task is to process data in their custody from the perspective of early side effect detection, towards an integrative system. To support some of the tasks of these partners, additional expertise on the extraction and interpretation of clinical data for detection of suspected ADRs has been also incorporated (partner LSHTM and its subcontractor ICL).

The second set of participants involves those parties who are currently involved in spontaneous reporting systems of ADRs (NEUROLESI, UB2). They therefore have a detailed know-how on the pro's and cons of spontaneous reporting systems. It is their day-to-day task to assess signals that could point to potential side effects of drugs. In this project, they provide the expertise to judge whether or not the automated analysis of EHRs for detection of possible side effects of drugs constitutes an improvement over current spontaneous reporting systems. As a result, their focus will be on the development of validations sets and coordinating the evaluation.

The third set of participants are those parties that have experience in understanding the molecular, biological and genetic mechanisms involved in side effects (UPF, and its subcontractor TAU, AZ and USC) – they are well equipped to assess whether a signal can be explained by our current understanding of biological mechanisms. As researchers or commercial partners, they conduct investigations once a signal has been reported. Their focus in this proposal will be the interpretation of a signal in the light of our current biomedical knowledge.

The fourth set of participants is formed by those parties that have experience in using ICT to build integrated systems (UAVR, EMC). These parties are well equipped to develop systems that in one hand present a uniform user interface, and on the other hand deal with a variety of systems that need to be accessed. Their focus in this proposal is to bring about a single system from the end-user's perspective and, at the same time, provide solutions for dealing with a variety of underlying systems. Nevertheless, technological integration has as a pre-requisite expert judgement in the optimal way to combine the different sources of evidence contemplated in the project; representing one of the main target groups of users, a top international pharmaceutical company is an ideal candidate for this role (AZ).

Finally, a partner with specific expertise on management, dissemination and exploitation of research projects (FIMIM) was deemed necessary to ensure that these tasks were undertaken professionally.

Although the description above focuses on the main profiles and areas of expertise of each partner, the work plan has been built with interdisciplinary collaboration as one of the main strengths and drivers of the project. Therefore, the involvements of partners in the different tasks have been agreed upon taking into account the diverse, valuable contributions that each partner could make to the whole range of activities foreseen. This results in an optimally populated Responsibility Assignment Matrix, in which expertise and capabilities of all participants are intended to be taken advantage of for maximum global effect.

Given the diversity of participants, cohesion needs to be fostered. In this proposal, two mechanisms will be deployed to create cohesion. First, specific validation sets of both confirmed ADRs and spurious signals will be used by all partners to steer their effort; their activities will be focused on these validation sets. Although each partner brings his/her own contribution according to expertise, the final yardstick will be these validation sets. Second, by insisting that at the end of the day an integrated system will be available to present the final results, coherence will be fostered between diverse settings (e.g. the terminology mapping that "unites" various databases).

A significant part of the Consortium has previously worked together in European projects (most recently, the INFOBIOMED Network of Excellence involving partners EMC, FIMIM, UAVR and AZ, and a number of researchers of partner UPF). In those projects the partners have learned to appreciate each others' strengths (and weaknesses). That collaboration has proven successful both in terms of publications originating from that network as well as practical experience in communicating across different disciplines. That experience forms an important basis for further collaboration in this project.

i) Sub-contracting

Due to the fact that the overall goal of the ALERT project will be the development of an engine that automatically exploits data from electronic health records and connects it with supporting biomedical evidence for the early detection of adverse drug reactions, the ALERT Consortium envisaged the collaboration of relevant third parties, with significant expertise in the field, that would raise the proficiency and level of the final outcome of the project. Three third parties have been thus asked to participate as subcontractors in the ALERT project.

None of the subcontractors will be responsible of the activities presented in this proposal, as their involvement refers to complementary expertise that is not at the core of the scientific and technological work in the project. However, their contribution is extremely valuable and will significantly bolster the Consortium capabilities. Their role will be related to the accession of EHR databases, data and text mining techniques, ethical regulations and specific expertise in particular areas (e.g. in the domain of pharmacogenetics, molecular modelling, etc.).

A short description of each subcontractor, including the activities in which they will be involved, and their estimated costs, is presented hereinafter.

Subcontractors of partner **UPF**:

- Dr. David Gurwitz and his team at Tel-Aviv University **(TAU)** will provide the ALERT consortium with advice on the pharmacogenetics component of the drug adverse events. Dr. Gurwitz is an internationally recognised expert in this field. He is an affiliate member of the Pharmacogenomics Research Network (PGRN) and the associate editor of the Pharmacogenomics journal. Specifically, TAU will contribute to the following activities: 2.3

Terminology Mapping, 4.1 DB and Literature Mining, 6.2 Prospective Validation and 7.2 Dissemination Activities. Estimated costs for this subcontractor are 65,872 Euro.

Subcontractors of partner **NEUROLESI**:

- Dr Giampiero Mazzaglia and his group settled in Florence (Health Search, of the Italian College of General Practitioners) **(SIMG)** will provide the ALERT consortium with: a) expertise in conducting epidemiologic investigations on drug safety through general practice databases; b) electronic medical data from the Health Search database to be explored through text and data mining techniques (WP3). Due to their expertise on the use of EHR, they will also contribute to the implementation of ethical surveillance (activity 1.3), terminology mapping (activity 2.3), retrospective and prospective validation (activities 6.1 and 6.2), and dissemination activities (task 7.2). Estimated costs for this subcontractor are 162,035 Euro.

Subcontractors of partner **LSHTM**:

- Prof. Azeem Majeed and his group at Imperial College London **(ICL)** will provide expertise in the extraction and use of primary care and secondary care data sets and will contribute to the definition of a mapping scheme of different database specific terminologies (activity 2.3). Prof. Majeed, who is an internationally recognised expert in this area, will also contribute to activity 3.3 Data mining and to 6.1 Prospective Validation. Finally, ICL will be asked to contribute to dissemination activities. Estimated costs for this subcontractor are 72,957 Euro.

ii) Other countries

N/A

iii) Third parties

N/A

B 2.4 Resources to be committed

ALERT is a very ambitious project, with 8 work packages deeply interrelated (see PERT diagram on section 1.3 above) and 23 activities. The Consortium involves fifteen renowned institutions, one of them a major pharmaceutical company, who will be required to intensively interact in pursue of the overall goals. In addition, three subcontractors are also expected to contribute to various tasks. Since the project aims at making a major and durable impact in this strategically critical field, important efforts have to be devoted to the connection with other projects and to ensure that the quality of the results is exceptional, so that the community embraces the initiative and allows the project to achieve its ultimate objectives.

Since most participants are already actively involved in the ADR domain, hence having access to relevant databases, software, equipment and facilities needed to carry out the work, the financial plan for ALERT relies on strong involvement of expert personnel on each of the participating institutions, for a total effort of 800.4 person-months (pm). In consequence, personnel costs are the main category in the budget, representing 53.2% of the total costs of the project.

To ensure maximum efficiency, efforts in the work plan have been carefully adjusted at the Work Package and Activity levels, using several instances of a Responsibility Assignment Matrix (RAM). The estimation has been refined through a significant number of iterations to ensure that the effort allocations were both faithful and globally coherent according to the intensity and complexity of the tasks to be carried out, taking also into account the time schedule of each activity and the need for overall consistency. The overall percentages of effort assigned to the different WPs are:

WP	% effort	Type
1	5.0	RTD
2	5.0	RTD
3	30.0	RTD
4	20.0	RTD
5	15.0	RTD
6	13.0	RTD
7	5.0	OTHER
8	7.0	MGT

Personnel costs have been calculated by asking each partner to estimate a faithful average pm cost, weighted according to the different types of personnel to be involved in the work, according also to each institution's policy. This results in a total personnel budget of 3,130,367 Euro.

Other direct costs included in the budget are mainly reckoned to cover travel expenses and minor equipment and consumables costs. A common policy for the whole Consortium has been followed to estimate the minimum necessary for these, resulting in an estimation of 6,000 Euro/year per participant to encompass the attendance to project meetings (average of three meetings per year) plus minor equipment and consumables. Due to the need for more personal interaction with partners as they supervise their work packages, Work Package Leaders have been allocated an extra 3000 Euro/year for a total of 9,000 Euro/year. The

Project Co-ordinator (EMC) has also been allocated an extra 40,000 Euro amount for the whole project, so that expenses related to external parties (Scientific Advisory Board, ad-hoc committees, relevant stakeholders that need to be involved as experts, representatives of other international and local initiatives that need to be actively enrolled) and other expenses belonging to the Consortium as a whole (such as organisation of workshops or printing of dissemination materials, etc.) are properly covered. In order to participate in and/or organise clustering and concertation activities with other projects and initiatives in the field, an extra 90,000 Euro amount has been allocated to the Project Co-ordinator (EMC), representing a 2% of the overall funding. This all results in a total budget for other direct costs of 411,710 Euro, representing 7.0% of the total costs of the project.

More importantly, three subcontractors have been also asked to participate, in order to provide key complementary expertise in several activities. Subcontracting costs have been estimated in a similar fashion as partners, on the basis of expected effort, estimated at the activity level, and using reasonable personnel rates, it all resulting in a total amount of 300,864 Euro, representing 5.1% of the total costs. This budget has been allocated under RTD activities. Budget has been allocated as well for the provision of financial statements (audit certificates, certificates on the methodology, etc). An estimation of 1,701 Euro per audit certificate has been used, and the number of certificates needed per partner has been calculated taking into account that one certificate is expected to be needed each time the funding requested equals or surpasses 375,000 Euro. Following this guidance principle, four participants have been allocated budget, and it has been allocated as subcontracting costs under Management activities, since most participants are expected to use external audit companies for these purposes. This results in 8,505 Euro, representing 0.1% of the total costs.

Finally, overheads have been calculated using the policy applicable for each institution, which in general means using the special transition flat-rate of FP7 (as most partners are of academic nature), with the only exception of participant AZ, which will use the standard flat rate. This results in a total of 2,029,154 Euro for overheads, representing 34.5% of the total budget.

The resulting total budget amounts 5,880,600 Euro, of which the EC contribution requested is 4,500,000 Euro. The calculation of the funding takes into account that the different types of activity have different reimbursement rates in FP7; “Management” activities are funded 100%, whereas “RTD” activities are funded 50% or 75% depending on the type of institution. Efforts (and thus personnel costs) have been allocated to one or the other type of activity according to the WP they belong to (see table above); other direct costs have been proportionately assigned to one or the other type of activity proportionately to the effort allocation.

It is worthwhile to remark that, aside from committing the 1,380,080 Euro not covered by the EC contribution with own resources, the Consortium will also contribute numerous other resources to the project in terms of: access to and maintenance of the EHRs and pharmacovigilance databases (PEDIANET, Health Search, Regional SISR Data, IPCI, PHARMO, QRESEARCH, Aarhus University Hospital Database, Pharmacological Activity databases at participant AZ, GIF-Gruppo Interregionale di Farmacoviglanza database), and software licenses (bioinformatics and chemoinformatics software, Stata 9, SAS and Peregrine Software), the total value of which can be estimated in excess of 5,000,000 Euro, of which around 1,200,000 Euro will be the part associated with project use, plus other resources such us: Data Center with 2 rack units and 10 processing servers (Linux and Windows2003); computer network facilities; technical support personnel; server/hardware maintenance; NHS net connection charges; database software (DBMS); SQLServer; MSDN, etc., to mention only the most significant.

B3. Impact

B 3.1 Strategic impact

The ALERT project addresses the **ICT-2007.5.2a)** ("**Advanced computerised adverse event systems**") objective within the **ICT** Work Programme. This objective is primarily addressed to:

> *"Identification of common patterns in safety-relevant events beyond merely reporting nosocomial infections and/or Adverse Drug Events (ADE). These alerting and management support systems must incorporate new tools for prediction, detection and monitoring of adverse events and other relevant events impacting on patient safety."*

As explained in this proposal, the development of new systems for early detection of Adverse Drug Events (ADE) using innovative technologies is precisely the core of the ALERT proposal. The huge Electronic Healthcare Record (EHR) databases used in the project for signal generation are complemented with evidence-based signal substantiation using various biomedical knowledge sources and *in silico* simulations, so that all available information is taken into account by the developed tools; this is bound to boost the ability to detect potential ADE at an early stage. Additionally, the system resulting from ALERT will be also of use for monitoring and even predict the onset of ADE.

The objective addressed in the Work Programme also mentions that solutions devised:

> *"(...) should be based on innovative data mining, integration techniques of existing databases and electronic health record systems (...) Emerging technologies like semantic mining and semantic information integration should be validated on multimedia databases."*

Text and data mining of extensive EHR databases is one of the elements in ALERT; additionally, mapping, federation and integration of these databases at the nomenclature level are essential components foreseen in the work plan as cornerstones for further system development. Other databases, especially those related with scientific biomedical literature, are used to complement the capabilities of the system to make it a uniquely powerful tool for ADE detection. Both semantic mining and semantic information integration are thus lying at the core of the ALERT strategy for the fulfilment of its ultimate objective.

It is also to be remarked that the work programme requests proposals to:

> *" (...) include a validation scheme leading to quantitative benefits."*

Validation plays a crucial role in ALERT. Both retrospective and prospective validation activities are included in the project. Of special interest for comparative estimation of the benefits of ALERT is the retrospective strategy, in which a certain point in time will be artificially re-created in the databases of reference in order to reproduce the "state-of-the-art" before several specific, important ADE were found and officially reported. Running the ALERT system against the scenario "as it was then" is expected to prove that, with ALERT, the ADE would have been found earlier on, and to quantify this improvement. Both accuracy and comprehensiveness of the system will be evaluated. Since the project will follow an

iterative development scheme, several validation cycles will be run throughout the project and fed back into design and development for system optimisation.

All of the above shows that ALERT extensively matches the target outcome expected from objective **ICT-2007.5.2a)**.

On the other hand, the successful completion of the ALERT project, and its derived set of innovative tools that dynamically integrate multiple data sources for intelligent, early detection of adverse events, can also help objective **ICT-2007.5.2b) ("New risk prediction for large scale events")**:

> *" (...) research in new risk prediction, assessment and management tools for preparation, surveillance, support and intervention in case of large-scale adverse health events."*

Therefore, the ALERT project is expected to significantly contribute to the majority of impacts expected from objective **ICT-2007.5.2: Advanced ICT for Risk Assessment and Patient Safety**:

- *"World-leading levels of patient safety with fewer medical errors and optimised medical interventions resulting in savings of lives and resources."*
- *"Early alerts and improved management of large scale health-related crises through effective and automated risk prediction, assessment and management."*
- *"Accelerated and wider adoption of future electronic health record systems."*

By facilitating the early detection of ADE, and providing key information on populations at risk, potential drug interactions, potential underlying mechanisms and intervening pathways in adverse events, etc., the ALERT project will allow for improved and more complete information to be available for drug and healthcare delivery, leading to increased patient safety and its associated cost savings. The project targets both the healthcare and research communities, and regulatory authorities, and aims in essence to constitute an automated risk assessment instrument focused on unexpected effects of marketed drugs. Being conceived as automatic and dynamic, the ALERT system is also expected to help the continuing monitoring and management of adverse drug events, in ways that spontaneous reporting and other current systems can only marginally reproduce. Should the system be widespread and demonstrably useful, it has the potential to contribute to the development of future electronic health record systems, insofar as the expected benefits of these innovative IT tools are only fully attainable when EHRs develop themselves in consistency, richness and formats that allow them to be subject of such tools. In anticipation, ALERT has been designed to be modular and scalable, so that different EHR databases (other than those participating in the Consortium) can be progressively "enlisted" in the future, adopt the software for data extraction and therefore become susceptible of exploitation by the system, for maximum global effect.

On a more general level, it can also be mentioned that ALERT contributes to a number of the impacts related to Challenge 5 ("**Towards sustainable and personalised healthcare** ") of the ICT Work Programme:

> *"(...) delivering quality healthcare to all its citizens, at affordable cost".*

> *"(…) a change in the way (…) medical knowledge is managed and transferred to clinical practice."*

The way ALERT is bound to enable early detection of ADE implies quicker solutions to important and costly healthcare problems. The project will also represent an excellent proof on how innovative IT tools can manage existing biomedical knowledge more comprehensively and efficiently, allowing for faster, direct transfer of scientific and medical evidence to patient safety and, thus, health benefit. The capabilities to automatically extract knowledge from clinical databases, considering patient segmentation, can also contribute to:

> *"(…) personalisation of care that open new opportunities in health and disease management"*

And, by coupling mining of EHRs with study of underlying mechanisms, ALERT also offers an inclusive solution that combines:

> *"(…) knowledge about diseases that ranges from molecular to organ and system levels",*

helping the development of:

> *" (…) a new generation of predictive medicine."*

Notably, the ALERT project is focused and will directly contribute to:

> *"(…) health information processing and quicker transfer of knowledge to clinical practice."*

And, by making ADE known earlier and facilitating their monitoring and management, the success of ALERT will likely contribute to:

> *"Savings in lives and resources by focusing on prevention and prediction rather than on costly medical interventions after symptoms and diseases have developed."*

All in all, the project is centred on providing:

> *"Higher patient safety by optimising medical interventions and preventing errors.",*

especially as regards to sub optimal drug prescription and dosage resulting from incomplete or hampered access to the wealth of biomedical knowledge available.

Finally, and as mentioned above, the strong validation scheme of ALERT complies with another of the key requirements:

> *"Validation should include quantitative indicators of the added value and potential impact of the proposed applications."*

For such an endeavour, it is important to realise that the **European dimension** is key, because the subject of the project can only be appropriately tackled at the European level; its solution

depends on the interplay of a significant number of key, relevant actors that commit to a joint effort, surpassing their individual perspectives. In this sense, the need to integrate a huge amount of information from diverse EHR, literature and scientific databases is crucial to develop a system with the desired specificity and sensitivity. A national or local effort would be quite insufficient for this purpose, both in terms of scale of resources needed but also in terms of the amounts of data that would have to be gathered for proper validation. The project has raised the interest and commitment of two national regulatory authorities on the subject (Spain, Netherlands), which have agreed to be part of the Scientific Advisory Board of ALERT, and established links with the European Medicines Evaluation Agency (EMEA) for collaboration in the framework of the project. In this way, the project ensures that the needs of one of the key stakeholders in the area are always adequately considered. To further maximise its impact in the area concerned, the project will reach out to several of the key European initiatives in the field, and its active dissemination policy will aim at enabling links with many others at the international level. Finally, the design of the project takes into account the modularity and scalability of the software to be produced (especially regarding knowledge extraction tools of EHR databases), so as to facilitate its use by other adopters, and its application to a wider list of adverse events/drugs, for global maximum impact.

It is important to note that the achievement of some of the desired impacts, as described in this section, is subject to a number of risks, as described in section 1.3 of this proposal. To cope with this factor, and ensure that expected impacts are effectively attained, the ALERT work plan comprises both strong project management tasks (WP8) that include active risk management, but also a specific assessment activity in WP1 that will continually review the progress achieved and measure it against the goals set. As said above, the validation activities undertaken in the framework of WP7 will provide invaluable insight into the added value of the project compared to systems currently in use, offering a way to measure the impact of ALERT as regards to the speed and precision with which ADE are to be predicted, detected and monitored in Europe in the coming years.

B 3.2 Plan for the use and dissemination of foreground

Dissemination and exploitation are important activities for ALERT, as the ultimate success of the project in the longer term depends on its ability to engage different stakeholders and become a sustainable activity. Therefore, the work plan devotes a whole work package (WP7) to these activities.

A solid and comprehensive ***dissemination plan*** is required to be undertaken within the framework of ALERT in order to raise awareness of the project as a whole, and specifically of its results, among different stakeholders (the European Commission, regulatory authorities, healthcare institutions and professionals, scientific community, pharmaceutical companies, and the general public are the main, key actors expected to be targeted).

To this end, WP7 contributors will focus initially on developing a communication plan for publicizing the project and its results, thereby establishing a consistent strategy for maximizing the impact of all communication efforts. This will fully define and formalise four basic pillars of the ALERT communication strategy: i) definition of the communication objectives; ii) identification of target audiences; iii) description of the dissemination actions to be tackled; iv) identification of the specific tools to be used/developed in order to support effective communication.

Afterwards, the communication tools identified by the communication plan will be developed as needed, keeping in mind the actions, audiences and objectives to which these tools should serve as supporting materials. The bulk of these dissemination undertakings will entail primarily, though not exclusively, scientific interactions that will include, at least:

- *Publication of scientific papers.* Preference will be given to the generation of publications related with the project activities and results, which will be mainly submitted for publication in international scientific journals with as high impact as possible.
- *Presentations at relevant events (congresses, meetings, workshops, etc.).* An important dissemination activity will comprise participation or organisation in events where the presentation of the ALERT project, its approaches and results, and consultations with other external actors, can take place. Presentations can take the form of oral communications, participation in poster sessions or any other format foreseen as appropriate. The SC and SAB will be allowed to provide guidance for identifying the key relevant events in which the project should be present, in the light of academic, political and/or industrial relevance. WP7 will prepare guidelines for homogeneous presentations by all ALERT participants (power point templates, poster layouts, etc.). After 18 months, ALERT will organise a workshop to present the first results and a number of organizations from different fields, such us authorities, industry or professional bodies, will be invited to participate.
- *Individual presentations and meetings with key stakeholders.* To raise the interest and gain support of key actors in the field, such as regulatory authorities, individual contacts will be established as needed.
- *Concertation activities*. ALERT will encourage all partners to actively participate in clustering and concertation activities with other projects in the field. The project will participate in regular concertation activities (at least two per year) with other ICT projects, which will be organised to facilitate exchange of information and good practice and to discuss topics of common interest to all relevant projects and/or other relevant stakeholders.
- Some tools considered essential will be developed in order to support and make the most out of the dissemination activities planned. A brochure will be produced, with the intention to support the presentations at events and the individual meetings carried out. A website will be set up, which will be intended to support and reinforce the rest of the above-mentioned dissemination activities. The website will initially include general information, for example: description, objectives, participants, results, activities, contact links, etc. Nevertheless, as the project evolves, the site will be connected with the web tools and software produced as a result of the project, so as to add a “thick” layer of content to any communication activity. This will be increasingly relevant as the project unfolds. A password-protected Intranet will be reserved for project participants, in order to facilitate document exchange and management tasks. An electronic newsletter may be developed too, to be sent to interested parties with the main achievements of the project with the objective to raise awareness of the ALERT developments on broad or targeted communities.

Exploitation activities are also centred in WP7, entailing the goal of maximising the use of the system and studying long-term sustainability.

The final outcome of ALERT is intended to be an open computerized system that automatically exploits data from electronic health records and couples it with supporting biomedical evidence for the early detection of adverse drug reactions. An exploitation strategy will be designed (activity 7.3) in order to attract different relevant stakeholders according to an in-depth analysis of the impact of the outcomes expected from the project, their added value and the main potential beneficiaries.

Exploitation activities will be developed during the last year of the project, once several of the foreseen milestones have been achieved, e.g. completion of some validation iterations in WP6, completion of core technical and scientific tasks in WP3 and WP4, etc. In this way, potential users and sponsors will be able to see preliminary results of the project and be provided with an appraisal of the comparative benefits, including insofar as possible economic impact. Key concepts of the project, such as the ability to inspect the underlying EHR data, relevant literature and information that was used to generate the signals, should be visible as well.

Primary stakeholders for exploitation activities are those that are expected to contribute, use and/or support (including financial contribution) the resulting system in the long term. Preliminary identification of these actors points to four basic profiles:

- Regulatory and other healthcare authorities.
- EHR database owners that can be “enlisted” and motivated to integrate their data systems into the global ALERT framework.
- Researchers in the field.
- Pharmaceutical companies.

The exploitation activity will be centered on studying different sustainability scenarios (including business planning as needed) for long term maintenance, enlargement and development of the ALERT system. The different stakeholders will be actively encouraged to participate in such debates, and in order to draw their attention to the needs and eventual benefits of the project, individual meetings will be fostered. The ALERT consortium will promote and host meetings with other parties, projects and initiatives that can be actively linked to the federation scheme proposed. The analysis of all of the information obtained from these contacts will be analysed and result in specific plans for the durability of ALERT beyond the period of EC funding.

It is important to mention that the exploitation activities will be bound to a solid strategy for knowledge management. Due to the fact that background owned by participants will have to be respected in any future exploitation scenario, IPR management will be carefully considered. Both background (e.g. existing databases and tools) used and foreground generated in the framework of the project (e.g. systems and tools developed in ALERT) will need to be identified, and access rights appropriately managed so that scientific work can develop without any obstacles, and plans for future exploitation are safeguarded. For this purpose, support to appropriate definition of ownership of the results, and identification of existing and potential exploitation models will be facilitated throughout the project, on the basis of the principles agreed in the Consortium Agreement that will be concluded before the project starts. An Exploitation Manager included in the Project Management office will be responsible of supervising and controlling all these issues until successful resolution can be obtained in every case.

Discussions on suitable exploitation models should be reinforced by encouraging results from the validation exercises. Potential scenarios will be discussed taking into account the normal working flow of the ALERT "engine", which depends on the degree of awareness raised among regulatory authorities as central stakeholder and on the number of EHR databases to become interested in the initiative and be actively linked to the federation scheme proposed. Visibility of the project, attention and positive reactions from other potential end-users (of clinical, academic and industrial nature) of the system will also be a key factor to take into account, and therefore analysis of the results of dissemination activities held will be important for the development of exploitation scenarios.

B4. Ethical issues

In this project, a total of 30 million patient records from eight different databases will be used. Clearly, a number of ethical issues are involved that deal with ethical, legal, and privacy issues.

As the project will not collect new data other than that made available by the participating databases, the cornerstone of ensuring proper ethical and legal conduct is located in the rules and regulations that govern each individual database that contributes patient records. These databases have a history of conducting studies and writing scientific papers. As a result, each database has experience in using patient data for research purposes. Because the databases are located in different countries, each database has to deal with a specific set of rules and regulations. Although framed in European law, exact implementation of European law may vary. As a result, each database has their own mechanisms for dealing with both European, national and local rules and regulations. For example, the Dutch IPCI database has as ingredients:

1. Anonymousness of patient identity in the system of the individual general practitioner (only the patient's physician is able to determine the identity of a patient)
2. Passive informed consent of the patient (posters in the waiting room of the general practitioner, a web-site for patients on the studies that are conducted)
3. A mechanism for withdrawing data of those patients who object to participating in the database
4. A mechanism for the general practitioner to prevent certain data to be entered in the database
5. A mechanism for both patient and general practitioner to block certain individuals
6. A mechanism to inform each participating physician and patient about each individual study
7. A mechanism for the general practitioner and patient to withdraw data from any study they feel uncomfortable with
8. A supervisory board that reviews each individual study application
9. A dedicated technical infrastructure that cannot be accessed from outside the research setting
10. A bi-annual assessment of all procedures given the Dutch privacy law

Although the exact implementation of the rules and regulations vary amongst different databases, they are overall similar: ensuring privacy, informing participating physicians and patients, review of studies, and regular checking of compliance with national and/or local constraints.

As the databases use the data in their custody intensively for research purposes, these rules and regulations that govern the use of data are "sacred" – in the context of this project, deviation from those rules and regulations will not be an option. In addition, journals will require detailed information on how the data are managed in order to publish papers that originate from that database.

In this context, we also want to emphasize that the “raw” patient data will not be shared on a European level. That is, data mining activities will be conducted locally, and only aggregated data will be made available to other parties in the Consortium.

In this project, we will include a specific task that will scrutinize the ethical issues involved. The first objective of that activity will be a comparison of the rules and regulations across the different databases. In addition, participants will review their own implementation of ethical issues in the light of European rules, and the project will continuously monitor any ethical concerns that may arise. In this context, the project will adhere to operational principles that are consistent with the Oviedo convention and the Helsinki declaration in its last 2002 amendment. This ensures that appropriate consent has been obtained for the envisaged use of data, prior to anonymization. Obtaining appropriate consent, however, is the responsibility of the original data generators. The transfer of data will only involve anonymized data in agreement with the definition given in the Council of Europe recommendation Rec(2006)4 of the Committee of Ministers to Member States. This use is in agreement with the EU directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data.

ETHICAL ISSUES TABLE

	YES	PAGE
Informed Consent	YES	31, 32, 33, 57, 58, 88, 89
• Does the proposal involve children?		
• Does the proposal involve patients or persons not able to give consent?		
• Does the proposal involve adult healthy volunteers?		
• Does the proposal involve Human Genetic Material?		
• Does the proposal involve Human biological samples?		
• Does the proposal involve Human data collection?		
Research on Human embryo/foetus		
• Does the proposal involve Human Embryos?		
• Does the proposal involve Human Foetal Tissue / Cells?		
• Does the proposal involve Human Embryonic Stem Cells?		
Privacy	YES	31, 32, 33, 57, 58, 88, 89
• Does the proposal involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)		
• Does the proposal involve tracking the location or observation of people?		
Research on Animals		
• Does the proposal involve research on animals?		
• Are those animals transgenic small laboratory animals?		
• Are those animals transgenic farm animals?		
• Are those animals cloned farm animals?		
• Are those animals non-human primates?		
Research Involving Developing Countries		
• Use of local resources (genetic, animal, plant etc)		
• Benefit to local community (capacity building i.e. access to healthcare, education etc)		
Dual Use		
• Research having direct military application		
• Research having the potential for terrorist abuse		
ICT Implants		
• Does the proposal involve clinical trials of ICT implants?		
I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL		

FP7 Grant Agreement - Annex II General Conditions

II.1. Definitions

1. "*access rights*" means licences and user rights to *foreground* or *background*;

2. "*affiliated entity*" means any legal entity that is under the direct or indirect control of a *beneficiary*, or under the same direct or indirect control as the *beneficiary*, control taking 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.

3. "*associated country*" means a *third country* which is party to an international agreement with the *Community*, under the terms or on the basis of which it makes a financial contribution to all or part of the Seventh Framework Programme;

4. "*background*" means information which is held by *beneficiaries* prior to their accession to this agreement, as well as copyrights or other intellectual property rights pertaining to such information, the application for which has been filed before their accession to this agreement, and which is needed for carrying out the *project* or for using *foreground*;

5. "*dissemination*" means the disclosure of *foreground* by any appropriate means other than that resulting from the formalities for protecting it, and including the publication of *foreground* in any medium;

6. "*fair and reasonable conditions*" means appropriate conditions including possible financial terms taking into account the specific circumstances of the request for access, for example the actual or potential value of the *foreground* or *background* to which access is requested and/or the scope, duration or other characteristics of the *use* envisaged;

7. "*foreground*" means the results, including information, whether or not they can be protected, which are generated under the *project*. Such results include rights related to copyright; design rights; patent rights; plant variety rights; or similar forms of protection;

8. "*use*" means the direct or indirect utilisation of *foreground* in further research activities other than those covered by the *project*, or for developing, creating and marketing a product or process, or for creating and providing a service;

9. "*third country*" means a State that is not a Member State;

10. "*irregularity*" means any infringement of a provision of *Community* law or any breach of obligation resulting from an act or omission by a *beneficiary* which has, or would have, the effect of prejudicing the general budget of the European Communities or budgets managed by them through unjustified expenditure;

11. "*public body*" means any legal entity established as such by national law, and international organisations;

12. A legal entity is qualified as "*non-profit*" when considered as such by national or international law;

13. "*research organisation* " means a legal entity established as a *non-profit* organisation which carries out research or technological development as one of its main objectives;

14. "*SMEs*" mean micro, small and medium-sized enterprises within the meaning of Recommendation 2003/361/EC in the version of 6 May 2003.

Part A IMPLEMENTATION OF THE *PROJECT*

SECTION 1 – GENERAL PRINCIPLES

II.2. Organisation of the *consortium* and role of *coordinator*

1. All the *beneficiaries* together form the *consortium*, whether or not they enter into a separate written *consortium agreement*. *Beneficiaries* are represented towards the *Commission* by the *coordinator*, who shall be the intermediary for any communication between the *Commission* and any *beneficiary*, with the exceptions foreseen in this *grant agreement*.

2. The *Community financial contribution* to the *project* shall be paid to the *coordinator* who receives it on behalf of the *beneficiaries*. The payment of the *Community financial contribution* to the *coordinator* discharges the *Commission* from its obligation on payments.

3. The *coordinator* shall:

a) administer the *Community financial contribution* regarding its allocation between *beneficiaries* and activities, in accordance with this *grant agreement* and the decisions taken by the *consortium*. The *coordinator* shall ensure that all the appropriate payments are made to the other *beneficiaries* without unjustified delay;

b) keep the records and financial accounts making it possible to determine at any time what portion of the *Community financial contribution* has been paid to each *beneficiary* for the purposes of the *project;*

c) inform the *Commission* of the distribution of the *Community financial contribution* and the date of transfers to the *beneficiaries*, when required by this *grant agreement* or by the *Commission*;

d) review the reports to verify consistency with the *project* tasks before transmitting them to the *Commission*;

e) monitor the compliance by *beneficiaries* with their obligations under this *grant agreement*.

The *coordinator* may not subcontract the above-mentioned tasks.

4. *Beneficiaries* shall fulfil the following obligations as a *consortium*:

a) provide all detailed data requested by the *Commission* for the purposes of the proper administration of this *project;*

b) carry out the *project* jointly and severally vis-à-vis the *Community,* taking all necessary and reasonable measures to ensure that the *project* is carried out in accordance with the terms and conditions of this *grant agreement.*

c) make appropriate internal arrangements consistent with the provisions of this *grant agreement* to ensure the efficient implementation of the *project*. When provided for in Article 1.4 these internal arrangements shall take the form of a written *consortium agreement* (the "*consortium agreement*"). The *consortium agreement* governs *inter alia* the following:

   i. the internal organisation of the *consortium* including the decision making procedures;

   ii. **rules on *dissemination* and *use*, and *access rights*;**

   iii. the distribution of the *Community financial contribution*;

   iv. **the settlement of internal disputes, including cases of abuse of power;**

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

d) engage, whenever appropriate, with actors beyond the research community and with the public in order to foster dialogue and debate on the research agenda, on research results and on related scientific issues with policy makers and civil society; create synergies with education at all levels and conduct activities promoting the socioeconomic impact of the research.

e) allow the *Commission* to take part in meetings concerning the *project*.

II.3. Specific performance obligations of each *beneficiary*

Each *beneficiary* shall:

a) carry out the work to be performed, as identified in Annex I. However, where it is necessary for the implementation of the *project* it may call upon third parties to carry out certain elements, according to the conditions established in Article II.7 or any special clause in Article 7. The *beneficiary* may use resources that are made available by third parties in order to carry out its part of the work;

b) ensure that any agreement or contract related to the project, entered into between the *beneficiary* and any third party contain provisions that this third party, including the auditor providing the certificate on the financial statements or on the methodology, shall have no rights vis-à-vis the *Commission* under this *grant agreement*;

c) ensure that the rights of the *Commission* and the Court of Auditors to carry out audits are extended to the right to carry out any such audit or control on any third party whose costs are reimbursed in full or in part by the *Community financial contribution*, on the same terms and conditions as those indicated in this *grant agreement*;

d) ensure that the conditions applicable to it under Articles II.4.4, II.10, II.11, II.12, II.13, II.14 and II.22 are also applicable to any third party whose costs are claimed under the *project* according to the provisions of this *grant agreement*;

e) ensure that the tasks assigned to it are correctly and timely performed;

f) inform the other *beneficiaries* and the *Commission* through the *coordinator* in due time of:

- the names of the person(s) who shall manage and monitor its work, and its contact details as well as any changes to that information;
- any event which might affect the implementation of the *project* and the rights of the *Community;*
- any change in its legal name, address and of its legal representatives, and any change with regard to its legal, financial, organisational or technical situation including change of control and, in particular, any change of status as regards *non-profit public bodies*, secondary and higher education establishments, *research organisations* and *SMEs*;
- any circumstance affecting the conditions of participation referred to in the *Rules for Participation*[1], the *Financial Regulation*[2] and its *Implementing Rules*[3] or of any requirements of the *grant agreement*, especially if and when any eligibility criteria cease(s) to be met during the duration of the *project.*

g) provide the *Commission* including the European Anti-Fraud Office (OLAF) and Court of Auditors directly with all information requested in the framework of controls and audits;

h) take part in meetings concerning the supervision, monitoring and evaluation of the *project* which are relevant to it;

i) take all necessary steps to avoid commitments that are incompatible with the obligations provided for in this *grant agreement* and inform the other *beneficiaries* and the *Commission* of any unavoidable obligations which may arise during the duration of the *grant agreement* which may have implications for any of its obligations under the *grant agreement;*

j) ensure that it complies with the provisions of the state aid framework;

k) carry out the *project* in accordance with fundamental ethical principles;

l) endeavour to promote equal opportunities between men and women in the implementation of the *project;*

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[1] European Parliament and Council Regulation (EC) No 1906/2006 of 18 December 2006 OJ L391, 30.12.2006, p.1 and Council Regulation (Euratom) No 1908/2006 of 19 December 2006 OJ L 400, 30.12.2006, p.1, corrigendum JO L 54, 22.2.2007, p. 4.

[2] Council Regulation (EC, Euratom) No 1605/2002 of 25 June 2002 OJ L 248, 16.9.2002, p. 1 as last amended by Council Regulation (EC, Euratom) N° 1995/2006 of 13 December 2006 (OJ L 390, 30.12.2006, p. 1) and subsequent modifications.

[3] Commission Regulation (EC, Euratom) No 2342/2002 of 23 December 2002 OJ L357, 31.12.2002, p.1, as last amended by Regulation (EC, Euratom) No 1248/2006 (OJ L 227, 19.8.2006, p. 3) and subsequent modifications.

m) have regard to the general principles of the Commission Recommendation of 11 March 2005 on the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers, in particular concerning the working conditions, transparency of recruitment processes, and career development of the researchers recruited for the *project*;

n) take every necessary precaution to avoid any risk of conflict of interest relating to economic interests, political or national affinities, family or emotional ties or any other interests liable to influence the impartial and objective performance of the *project.*

SECTION 2 – REPORTING AND PAYMENTS

II.4. Reports and deliverables

1. The *consortium* shall submit a **periodic report** to the *Commission* for each reporting period within 60 days after the end of each respective period. The reporting shall comprise:

   a) an overview, including a publishable summary, of the progress of work towards the objectives of the *project*, including achievements and attainment of any milestones and deliverables identified in Annex I. This report should include the differences between work expected to be carried out in accordance with Annex I and that actually carried out,

   b) an explanation of the use of the resources, and

   c) a financial statement, from each *beneficiary* together with a summary financial report consolidating the claimed *Community* contribution of all the *beneficiaries* in an aggregate form, based on the information provided in Form C (Annex VI) by each *beneficiary*.

2. The *consortium* shall submit a **final report** to the *Commission* within 60 days after the end of the *project*. The report shall comprise:

   a) a final publishable summary report covering results, conclusions and socio-economic impact of the *project*.

   b) a report covering the wider societal implications of the *project*, including gender equality actions, ethical issues, efforts to involve other actors and spread awareness as well as the plan for the *use* and *dissemination* of *foreground*.

3. The *coordinator* shall submit a report on the distribution of the *Community financial contribution* between *beneficiaries*. This report must be submitted 30 days after receipt of the final payment.

4. A **certificate on the financial statements** shall be submitted for claims of interim payments and final payments when the amount of the *Community financial contribution* claimed by a *beneficiary* under the form of reimbursement of costs is equal to or superior to EUR 375 000, when cumulated with all previous payments for which a certificate on the financial statements has not been submitted. This certificate must be forwarded in the form of a detailed description verified as factual by its external auditor (Form D - Annex VII). However, for *projects* of a duration of 2 years or less, the certificate on the financial statements shall be submitted only for claims on final payments when the amount of the *Community financial contribution* claimed by a *beneficiary*, in the form of reimbursement of costs, is equal to or superior to EUR 375 000 when cumulated with all previous payments.

Certificates on the financial statements shall certify that the costs claimed and the *receipts* declared during the period for which they are provided, as well as the declaration of the interest yielded by the pre-financing meet the conditions required by this *grant agreement*. Where third parties' costs are claimed under the *grant agreement*, such costs shall be certified in accordance with the provisions of this Article. The auditor shall include in its certificate that no conflict of interest exists between itself and the *beneficiary* in establishing this certificate.

The *Commission* may, at its sole discretion, accept at the request of a *beneficiary*, that it submits a **certificate on the methodology** for the calculation of costs, which it used to prepare its claims with regard to both personnel and indirect costs, and the related control systems. This certificate must be forwarded in the form of a detailed description verified as factual by its external auditor (Form E - Annex VII). When this certificate is accepted by the *Commission*, the requirement to provide an intermediate certificate on the financial statements for claims of interim payments shall be waived.

Certificates on the financial statements and on the methodology shall be prepared and certified by an external auditor and shall be established in accordance with the terms of reference attached as Annex VII to this *grant agreement*. Each *beneficiary* is free to choose any qualified external auditor, including its usual external auditor, provided that the cumulative following requirements are met:

i) the auditor must be independent from the *beneficiary*;

ii) the auditor must be qualified to carry out statutory audits of accounting documents in accordance with national legislation implementing the 8th Council Directive on statutory audits of annual accounts and consolidated accounts[4] or any *Community* legislation replacing this Directive. *Beneficiaries* established in *third countries* shall comply with national regulations in the same field and the certificate on the financial statement provided shall consist of an independent report of factual findings based on procedures specified by the *Community*.

Public bodies, secondary and higher education establishments and *research organisations* may opt for a competent public officer to provide their certificate on the financial statements and on the methodology, provided that the relevant national authorities have established the legal capacity of that competent public officer to audit that entity and that the independence of that officer, in particular regarding the preparation of the financial statements, can be ensured.

Certificates by external auditors according to this Article do not affect the liability of *beneficiaries* nor the rights of the *Community* arising from this *grant agreement*.

5. The *consortium* shall transmit the reports and other deliverables through the *coordinator* to the *Commission* by electronic means. In addition, Form C, must be signed by the authorised person(s) within the *beneficiary*'s organisation, and the certificates on the financial statements and on the methodology must be signed by an authorised person of the auditing entity, and the originals shall be sent to the *Commission*.

[4] Directive 2006/43/EC of the European Parliament and of the Council of 17 May 2006 on statutory audits of annual accounts and consolidated accounts, amending Council Directives 78/660/EEC and 83/349/EEC and repealing Council Directive 84/253/EEC

6. The layout and content of the reports shall conform to the instructions and guidance notes established by the *Commission*.

7. The reports submitted to the *Commission* for publication should be of a suitable quality to enable direct publication and their submission to the *Commission* in publishable form indicates that no confidential material is included therein.

8. Deliverables identified in Annex I shall be submitted as foreseen therein.

9. The *Commission* may be assisted by external experts in the analysis and evaluation of the reports and deliverables.

II.5. Approval of reports and deliverables, time-limit for payments

1. At the end of each reporting period, the *Commission* shall evaluate *project reports and deliverables* required by the provisions of Annex I and disburse the corresponding payments within 105 days of their receipt unless the time-limit, the payment or the *project* has been suspended.

2. Payments shall be made after the *Commission's* approval of reports and/or deliverables. The absence of a response from the *Commission* within this time-limit shall not imply its approval. However, the *Commission* should send a written reply to the *consortium* in accordance with paragraph 3. The *Commission* may reject reports and deliverables even after the time-limit for payment. Approval of the reports shall not imply recognition of their regularity or of the authenticity of the declarations and information they contain and do not imply exemption from any audit or review.

3. After reception of the reports the *Commission* may:

   a) approve the reports and deliverables, in whole or in part or make the approval subject to certain conditions.

   b) reject the reports and deliverables by giving an appropriate justification and, if appropriate, start the procedure for termination of the *grant agreement* in whole or in part.

   c) suspend the **time limit** if one or more of the reports or appropriate deliverables have not been supplied, or are not complete or if some clarification or additional information is needed or there are doubts concerning the eligibility of costs claimed in the financial statement and/or additional checks are being conducted. The suspension will be lifted from the date when the last report, deliverable or the additional information requested is received by the *Commission*, or where the *Commission* decides to proceed with an interim payment in part in accordance with paragraph 4.

      The *Commission* shall inform the *consortium* in writing via the *coordinator* of any such suspension and the conditions to be met for the lifting of the suspension.

      Suspension shall take effect on the date when notice is sent by the *Commission*.

   d) suspend **the payment** at any time, in whole or in part for the amount intended for the *beneficiary(ies)* concerned:

      - if the work carried out does not comply with the provisions of the *grant agreement*;

- if a *beneficiary* has to reimburse to its national state an amount unduly received as state aid;

- if the provisions of the *grant agreement* have been infringed or if there is a suspicion or presumption thereof, in particular in the wake of any audits and checks provided for in Articles II.22 and II.23.;

- if there is a suspicion of *irregularity* committed by one or more *beneficiary(ies)* in the performance of the *grant agreement*;

- if there is a suspected or established *irregularity* committed by one or more *beneficiary(ies)* in the performance of another *grant agreement* funded by the general budget of the European Communities or by budgets managed by them. In such cases, suspension of the payments will occur where the *irregularity* (or suspected *irregularity*) is of a serious and systematic nature which is likely to affect the performance of the current *grant agreement*.

When the *Commission* suspends the payment the *consortium* shall be duly informed of the reasons why payment in whole or in part will not be made.

4. The *Commission* may proceed with an interim payment in part if some reports or deliverables are not submitted as required, or only partially or conditionally approved. The reports and deliverables due for one reporting period which are submitted late will be evaluated together with the reports and deliverables of the next reporting period.

5. On expiry of the time-limit for approval of the reports and payments, and without prejudice to suspension by the *Commission* of this time-limit, the *Commission* shall pay interest on the late payment, according to the conditions foreseen in the *Financial Regulation* and its *Implementing Rules*, at the rate applied by the European Central Bank for its main refinancing operations in euros, plus three and a half points. The reference rate to which the increase applies shall be the rate in force on the first day of the month of the final date for payment, as published in the C series of the Official Journal of the European Union.

   This provision shall not apply to *beneficiaries* that are *public bodies* of the Member States of the European Union.

   Interest on late payment shall cover the period from the final date of the period for payment, exclusive, up to the date when the payment is debited to the *Commission's* account, inclusive. The interest shall not be treated as a *receipt* for the *project* for the purposes of determining the final grant. Any such interest payment is not considered as part of the *Community financial contribution*.

6. The suspension of the time-limit, of payment or of the project by the *Commission* may not be considered as late payment.

7. At the end of the *project*, the *Commission* may decide not to make the payment of the corresponding *Community financial contribution* subject to one month's written notice of non-receipt of a report, of a certificate on the financial statements or of any other *project* deliverable.

8. The *Commission* shall inform the *coordinator* of the amount of the final payment of the *Community financial contribution* and shall justify this amount. The *coordinator* shall have two months from the date of receipt to give reasons for any disagreement. After the end of this period such requests will no longer be considered and the *consortium* is deemed to have

accepted the *Commission*'s decision. The *Commission* undertakes to reply in writing within two months following the date of receipt, giving reasons for its reply. This procedure is without prejudice to the *beneficiary's* right to appeal against the *Commission's* decision.

II.6. Payment modalities

1. The *Commission* shall make the following payments:

   a) a **pre-financing** in accordance with Article 6,

   b) for *projects* with more than one reporting period, the *Commission* shall make **interim payments** of the *Community financial contribution* corresponding to the amount accepted for each reporting period.

   c) the *Commission* shall make a **final payment** of the *Community financial contribution* corresponding to the amount accepted for the last reporting period plus any adjustment needed.

   Where the amount of the corresponding *Community financial contribution* is less than any amount already paid to the *consortium*, the *Commission* shall recover the difference.

   Where the amount of the corresponding *Community financial contribution* is more than any amount already paid to the *consortium*, the *Commission* shall pay the difference as the final payment within the limit of Articles 5.1 and II.20.

2. The total amount of the pre-financing and interim payments shall not exceed 90% of the maximum *Community financial contribution* defined in Article 5.

3. Payments by the *Commission* shall be made in Euro.

4. Costs shall be reported in Euro. *Beneficiaries* with accounts in currencies other than the Euro shall report costs by using, either the conversion rate published by the European Central Bank that would have applied on the date that the actual costs were incurred, or its rate applicable on the first day of the month following the end of the reporting period. *Beneficiaries* with accounts in Euro shall convert costs incurred in other currencies according to their usual accounting practice.

5. The bank account mentioned in Article 5.3 shall allow that the *Community financial contribution* and related interest are identified. Otherwise, the accounting methods of the *beneficiaries* or intermediaries must make it possible to identify the *Community financial contribution* and the interest or other benefits yielded.

6. Any payment may be subject to an audit or review and may be adjusted or recovered based on the results of such audit or review.

7. Payments by the *Commission* shall be deemed to be effected on the date when they are debited to the *Commission*'s account.

SECTION 3 – IMPLEMENTATION

II.7. Subcontracting

1. A *subcontractor* is a third party which has entered into an agreement on business conditions with one or more *beneficiaries*, in order to carry out part of the work of the *project* without the direct supervision of the *beneficiary* and without a relationship of subordination.

   Where the *beneficiary* enters into a subcontract to carry out some parts of the tasks related to the *project*, it remains bound by its obligations to the *Commission* and the other *beneficiaries* under the *grant agreement* and retains sole responsibility for carrying out the *project* and for compliance with the provisions of the *grant agreement*.

   Provisions of this *grant agreement* applying to *subcontractors* shall also apply to external auditors who certify financial statements or a methodology.

2. Where it is necessary for the *beneficiaries* to subcontract certain elements of the work to be carried out, the following conditions must be fulfilled:

   - subcontracts may only cover the execution of a limited part of the *project*;

   - recourse to the award of subcontracts must be duly justified in Annex I having regard to the nature of the *project* and what is necessary for its implementation;

   - recourse to the award of subcontracts by a *beneficiary* may not affect the rights and obligations of the *beneficiaries* regarding *background* and *foreground;*

   - Annex I must indicate the tasks to be subcontracted and an estimation of the costs;

   Any subcontract, the costs of which are to be claimed as an eligible cost, must be awarded according to the principles of best value for money (best price-quality ratio), transparency and equal treatment. Subcontracts concluded on the basis of framework contracts entered into between a *beneficiary* and a *subcontractor*, prior to the beginning of the *project* in accordance with the *beneficiary's* usual management principles may also be accepted.

3. *Beneficiaries* may use external support services for assistance with minor tasks that do not represent per se *project* tasks as identified in Annex I.

II.8. Suspension of the *project*

1. The *coordinator* shall immediately inform the *Commission* of any event affecting or delaying the implementation of the *project*.

2. The *coordinator* can propose to suspend the whole or part of the *project* if *force majeure* or exceptional circumstances render its execution excessively difficult or uneconomic. The *coordinator* must inform the *Commission* without delay of such circumstances, including full justification and information related to the event, as well as an estimation of the date when the work on the *project* will begin again.

3. The *Commission* may suspend the whole or part of the *project* where it considers that the *consortium* is not fulfilling its obligations according to this *grant agreement*. The *coordinator* shall be informed without delay of the justification for such an event and the conditions necessary to reinstate the work again. The *coordinator* shall inform the other

beneficiaries. This suspension takes effect 10 days after the receipt of the notification by the *coordinator*.

4. During the period of suspension, no costs may be charged to the *project* for carrying out any part of the project that has been suspended.

5. The suspension of the whole or part of the *project* may be lifted once the parties to the *grant agreement* have agreed on the continuation of the project and, as appropriate, any necessary modification, including extension of the duration of the *project*, has been identified by means of a written amendment.

II.9. Confidentiality

1. During the *project* and for a period of five years after its completion or any other period thereafter as established in the *consortium agreement*, the *beneficiaries* undertake to preserve the confidentiality of any data, documents or other material that is identified as confidential in relation to the execution of the *project* ("*confidential information*"). The *Commission* undertakes to preserve the confidentiality of "confidential information" until five years after the completion of the *project*. Upon a duly substantiated request by a *beneficiary*, the *Commission* may agree to extend this period regarding specific confidential information.

   Where *confidential information* was communicated orally, its confidential character must be confirmed by the disclosing party in writing within 15 days after disclosure**.**

2. Paragraph 1 no longer applies where:

   - the *confidential information* becomes publicly available by means other than a breach of confidentiality obligations;

   - the disclosing party subsequently informs the recipient that the *confidential information* is no longer confidential;

   - the *confidential information* is subsequently communicated to the recipient without any obligation of confidence by a third party who is in lawful possession thereof and under no obligation of confidentiality;

   - the disclosure or communication of the *confidential information* is foreseen by other provisions of this *grant agreement* or the *consortium agreement*;

   - the disclosure or communication of *confidential information* is required by the national law of one of the *beneficiaries* and this exception to the confidentiality requirement is foreseen in the *consortium agreement*[5].

3. The *beneficiaries* undertake to use such confidential information only in relation to the execution of the *project* unless otherwise agreed with the disclosing party.

4. Notwithstanding the preceding paragraphs, the treatment of data, documents or other material which are classified ("*classified information*") or subject to security restrictions or

[5] As certain national laws (for example regarding freedom of information) may provide that proprietary information made available under a confidentiality requirement must nevertheless be made public in case access is requested, the *beneficiaries* should inform each other of the existence of such national laws and make appropriate arrangements in the *consortium agreement*.

export- or transfer- control, must follow the applicable rules established by the relevant national and *Community* legislation for such information, including the *Commission's* internal rules for handling *classified information*[6]. Where a *beneficiary* is established in a *third country*, any security agreements between that *third country* and the *Community* shall also apply.

II.10. Communication of data for evaluation, impact assessment and standardisation purposes

1. *Beneficiaries* shall provide, at the request of the *Commission*, the data necessary for:

   - the continuous and systematic review of the specific programme and the Seventh Framework Programme;

   - the evaluation and impact assessment of *Community* activities, including the *use* and *dissemination* of *foreground*.

   Such data may be requested throughout the duration of the *project* and up to five years after the end of the *project*.

   The data collected may be used by the *Commission* in its own evaluations but will not be published other than on an anonymous basis.

2. Without prejudice to the provisions regarding protection of *foreground* and confidentiality, the *beneficiaries* shall, where appropriate, during the *project* and for two years following its end, inform the *Commission* and the European standardisation bodies about *foreground* which may contribute to the preparation of European or international standards.

II.11. Information to be provided to Member States or Associated Countries

1. The *Commission* shall, upon request, make available to any Member State or *Associated country* any useful information in its possession on *foreground*, provided that the following cumulative conditions are met:

   - the information concerned is relevant to public policy;

   - the *beneficiaries* have not provided sound and sufficient reasons for withholding the information concerned;

   - the applicable *Community* law on *classified informatio*n does not prohibit such action.

2. As stipulated in the *Rules for Participation*, the provision of information pursuant to paragraph 1 shall not transfer to the recipient any rights or obligations and the recipient shall be required to treat any such information as confidential unless it becomes duly public, or it was communicated to the *Commission* without restrictions on its confidentiality.

[6] Commission Decision 2001/844/EC, ECSC, Euratom of 29 November 2001 OJ L 317, 3.12.2001, p. 1 (as last amended by Decision 2006/548/EC, Euratom, OJ L 215, 5.8.2006, p. 38).

II.12. Information and communication

1. The *beneficiaries* shall, throughout the duration of the *project*, take appropriate measures to engage with the public and the media about the *project* and to highlight the *Community* financial support. Unless the *Commission* requests otherwise, any publicity, including at a conference or seminar or any type of information or promotional material (brochure, leaflet, poster, presentation etc), must specify that the *project* has received *Community* research funding and display the European emblem. When displayed in association with a logo, the European emblem should be given appropriate prominence. This obligation to use the European emblem in respect of *projects* to which the [European Community] [European Atomic Energy Community] contributes implies no right of exclusive use. It is subject to general third-party use restrictions which do not permit the appropriation of the emblem, or of any similar trademark or logo, whether by registration or by any other means. Under these conditions, *beneficiaries* are exempted from the obligation to obtain prior permission from the *Commission* to use the emblem. Further detailed information on the EU emblem can be found on the Europa web page.

   Any publicity made by the *beneficiaries* in respect of the *project*, in whatever form and on or by whatever medium, must specify that it reflects only the author's views and that the *Community* is not liable for any use that may be made of the information contained therein.

2. The *Commission* shall be authorised to publish, in whatever form and on or by whatever medium, the following information:

   – the name of the *beneficiaries*;

   – contact addresses of *beneficiaries;*

   – the general purpose of the *project* in the form of the summary provided by the *consortium*;

   – the amount and rate of the *Community financial contribution* granted to the *project*;

   – the geographic location of the activities carried out;

   – the list of *dissemination* activities and/or of patent (applications) relating to *foreground*;

   – the details/references and the abstracts of scientific publications relating to *foreground* and, where provided pursuant to Article II.30.4, the published version or the final manuscript accepted for publication;

   – the publishable reports submitted to it;

   – any picture or any audiovisual or web material provided to the *Commission* in the framework of the *project*.

   The *consortium* shall ensure that all necessary authorisations for such publication have been obtained and that the publication of the information by the *Commission* does not infringe any rights of third parties.

   Upon a duly substantiated request by a *beneficiary*, the *Commission* may agree to forego such publicity if disclosure of the information indicated above would risk compromising the *beneficiary's* security, academic or commercial interests.

II.13. Processing of personal data

1. All personal data contained in the *grant agreement* shall be processed in accordance with Regulation (EC) No 45/2001 of the European Parliament and of the Council 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. Such data shall be processed by the Controller solely in connection with the implementation and follow-up of the *grant agreement* and the evaluation and impact assessment of *Community* activities, including the *use* and *dissemination* of *foreground*, without prejudice to the possibility of passing the data to the bodies in charge of a monitoring or inspection task in accordance with *Community* legislation and this *grant agreement*.

2. *Beneficiaries* may, on written request, gain access to their personal data and correct any information that is inaccurate or incomplete. They should address any questions regarding the processing of their personal data to the Controller. *Beneficiaries* may lodge a complaint against the processing of their personal data with the European Data Protection Supervisor at any time.

3. For the purposes of this *grant agreement*, the Controller identified in Article 8.4 shall be the contact for the *Commission*.

Part B FINANCIAL PROVISIONS

SECTION 1 – GENERAL FINANCIAL PROVISIONS

II.14. Eligible costs of the *project*

1. Costs incurred for the implementation of the *project* shall meet the following conditions in order to be considered eligible:

   a) they must be actual;

   b) they must be incurred by the *beneficiary*;

   c) they must be incurred during the duration of the *project*, with the exception of costs incurred in relation to final reports and reports corresponding to the last period as well as certificates on the financial statements when requested at the last period and final reviews if applicable, which may be incurred during the period of up to 60 days after the end of the *project* or the date of termination whichever is earlier;

   d) they must be determined in accordance with the usual accounting and management principles and practices of the *beneficiary*. The accounting procedures used in the recording of costs and *receipts* shall respect the accounting rules of the State in which the *beneficiary* is established. The beneficiary's internal accounting and auditing procedures must permit direct reconciliation of the costs and receipts declared in respect of the *project* with the corresponding financial statements and supporting documents;

   e) they must be used for the sole purpose of achieving the objectives of the *project* and its expected results, in a manner consistent with the principles of economy, efficiency and effectiveness;

f) they must be recorded in the accounts of the *beneficiary*; in the case of any contribution from third parties, they must be recorded in the accounts of the third parties*;*

g) they must be indicated in the estimated overall budget in Annex I.

Notwithstanding point a), *beneficiaries* may opt to declare average personnel costs if based on a certified methodology approved by the *Commission* and consistent with the management principles and usual accounting practices of the *beneficiary*. Average personnel costs charged to this *grant agreement* by a *beneficiary* having provided a certificate on the methodology are deemed not to significantly differ from actual personnel costs.

Such a certificate shall be issued in accordance with the provisions laid down in Article II.4 and the relevant part of Form E in Annex VII, unless it has already been submitted for a previous *grant agreement* under the Seventh Framework Programme and the methodology certified has not changed.

2. Costs incurred by third parties in relation to resources they make available free of charge to a *beneficiary*, can be declared by the *beneficiary* provided they meet the conditions established in paragraphs 1 and 3, *mutatis mutandis* and are claimed in conformity with Article II.17.

3. The following costs shall be considered as non-eligible and may not be charged to the *project*:

a) identifiable indirect taxes including value added tax,

b) duties,

c) interest owed,

d) provisions for possible future losses or charges,

e) exchange losses, cost related to return on capital,

f) costs declared or incurred, or reimbursed in respect of another *Community project*,

g) debt and debt service charges, excessive or reckless expenditure.

II.15. Identification of direct and indirect costs

1. Direct costs are all those eligible costs which can be attributed directly to the *project* and are identified by the *beneficiary* as such, in accordance with its accounting principles and its usual internal rules.

With regard to personnel costs, only the costs of the actual hours worked by the persons directly carrying out work under *the project* may be charged. Such persons must:

– be directly hired by the *beneficiary* in accordance with its national legislation,

– work under the sole technical supervision and responsibility of the latter, and

– be remunerated in accordance with the normal practices of the *beneficiary*.

Costs related to parental leave for persons who are directly carrying out the *project* are eligible costs, in proportion to the time dedicated to the *project*, provided that they are mandatory under national law.

2. Indirect costs are all those eligible costs which cannot be identified by the *beneficiary* as being directly attributed to the *project* but which can be identified and justified by its accounting system as being incurred in direct relationship with the eligible direct costs attributed to the *project*. They may not include any eligible direct costs.

   Indirect costs shall represent a fair apportionment of the overall overheads of the organisation. They may be identified according to one of the following methods:

   a) Based on actual indirect costs for those *beneficiaries* which have an analytical accounting system to identify their indirect costs as indicated above.

      For this purpose, a *beneficiary* is allowed to use a simplified method of calculation of its full indirect eligible costs at the level of its legal entity if this is in accordance with its usual accounting and management principles and practices. Use of such a method is only acceptable where the lack of analytical accounting or the legal requirement to use a form of cash-based accounting prevents detailed cost allocation. The simplified approach must be based on actual costs derived from the financial accounts of the last closed accounting year.

   b) A *beneficiary* may opt for a flat rate of 20% of its total direct eligible costs, excluding its direct eligible costs for subcontracting and the costs of resources made available by third parties which are not used on the premises of the *beneficiary*.

   c) *Non-profit public bodies*, secondary and higher education establishments, *research organisations* and *SMEs*, which, due to the lack of analytical accounting, are unable to identify with certainty their real indirect costs for the *project*, when participating in funding schemes which include research and technological development and demonstration activities, as referred to in the table of Article II.16, may opt for a flat-rate of 60% of the total direct eligible costs[7] excluding its direct eligible costs for subcontracting and the costs of resources made available by third parties which are not used on the premises of the *beneficiary*. If these *beneficiaries* change their status during the life of the *project*, this flat rate shall be applicable up to the moment they lose their status.

   In the case of coordination and support actions, the reimbursement of indirect eligible costs for every *beneficiary* may reach a maximum of 7% of the direct eligible costs, excluding its direct eligible costs for subcontracting and the costs of resources made available by third parties which are not used on the premises of the *beneficiary*.

3. The *beneficiary* shall apply the option chosen in all *grant agreements* under the Seventh Framework Programme.

   However, any *beneficiary* that has opted for the possibilities described in paragraphs 2b) and 2c) for reimbursement of its indirect costs in a previous *grant agreement* funded under the Seventh Framework Programme may opt in this *grant agreement* for one of the methods

[7] NOTE: The rate established in this indent will apply for grants awarded under calls for proposals closing before 1 January 2010. The *Commission* shall establish, for grants awarded under calls closing after 31 December 2009, an appropriate level of flat rate which should be an approximation of the real indirect costs concerned but not lower than 40%, at that moment a special clause will be adopted and inserted in subsequent grant agreements.

described in paragraph 2a). However, it must then use that method in subsequent *grant agreements* established under the Seventh Framework Programme.

II.16. Upper funding limits

1. For **research and technological development activities**, the *Community financial contribution* may reach a maximum of 50% of the total eligible costs.

   However, for *beneficiaries* that are *non-profit public bodies*, secondary and higher education establishments, *research organisations* and *SMEs*, the rate may reach a maximum of 75% of the total eligible costs. If these *beneficiaries* change their status during the life of the *project*, this reimbursement rate shall be applicable up to the moment they lose their status.

2. For **demonstration activities**, the *Community financial contribution* may reach a maximum of 50% of the total eligible costs.

3. For **coordination and support actions**, the *Community financial contribution* may reach a maximum of 100% of the total eligible costs.

4. For **other activities** not covered by paragraphs 1 and 2, *inter alia*, management activities, training, coordination, networking and *dissemination* (including publications), the contribution may reach a maximum of 100% of the total eligible costs.

Paragraphs 1 to 4 shall apply also in the case of *projects* where flat rate financing or lump sum financing is used for the whole or for part of the *project*.

5. **Management** of the *consortium* activities includes:

   – maintenance of the *consortium agreement*, if it is obligatory,

   – the overall legal, ethical, financial and administrative management including, for each of the *beneficiaries*, the obtaining of the certificates on the financial statements and on the methodology and costs relating to financial audits and technical reviews,

   – implementation of competitive calls by the *consortium* for the participation of new *beneficiaries*, where required by Annex I of this *grant agreement*,

   – any other management activities foreseen by the annexes, except coordination of research and technological development activities.

6. For **training activities**, the salary costs of those being trained are not eligible costs under this activity.

The table illustrates the maximum rates of *Community financial contribution* for the activities relating to the funding schemes below:

Maximum reimbursement rates	Research and technological development activities (*)	Demonstration activities	Other activities
Network of excellence	50% 75% (**)		100%
Collaborative *project* (****)	50% 75% (**)	50%	100%
Coordination and support action			100% (***)

(*) Research and technological development includes scientific coordination.
(**) For *beneficiaries* that are *non-profit public bodies*, secondary and higher education establishments, *research organisations* and *SMEs*
(***) The reimbursement of indirect eligible costs, in the case of coordination and support actions, may reach a maximum 7% of the direct eligible costs, excluding the direct eligible costs for subcontracting and the costs of resources made available by third parties which are not used on the premises of the *beneficiary*.
(****) Including research for the benefit of specific groups (in particular SMEs)

II.17. Receipts of the *project*

Receipts of the *project* may arise from:

a) Resources made available by third parties to the *beneficiary* by means of financial transfers or contributions in kind which are free of charge:

   i. shall be considered a *receipt* of the *project* if they have been contributed by the third party specifically to be used on the *project*;

   ii. shall not be considered a *receipt* of the *project* if their use is at the discretion of the *beneficiary's* management.

b) Income generated by the *project*:

   i. shall be considered a *receipt* for the *beneficiary* when generated by actions undertaken in carrying out the *project* and from the sale of assets purchased under the *grant agreement* up to the value of the cost initially charged to the *project* by the *beneficiary*;

   ii. shall not be considered a *receipt* for the *beneficiary* when generated from the *use* of *foreground* resulting from the *project.*

II.18. *Community financial contribution*

1. The "*Community financial contribution*" to the *project* shall be determined by applying the upper funding limits indicated in Article II.16, per activity and per *beneficiary* to the actual eligible costs and/or to the flat rates and/or lump sums accepted by the *Commission*.

2. The *Community financial contribution* shall be calculated by reference to the cost of the project as a whole and its reimbursement shall be based on the accepted costs of each *beneficiary*.

3. The Community financial contribution cannot give rise to any profit for any *beneficiary*. For this purpose, at the time of the submission of the last financial statement, the final amount of the *Community financial contribution* will take into account any *receipts* of the *project* received by each *beneficiary*. For each *beneficiary*, the *Community financial contribution* cannot exceed the eligible costs minus the *receipts* for the *project*.

4. The total amount of payments by the *Community* shall not exceed in any circumstances the maximum amount of the *Community financial contribution* referred to in Article 5.

5. Without prejudice to the right to terminate the *grant agreement* under Article II.38, and without prejudice to the right of the *Commission* to apply the penalties referred to in Articles II.24 and II.25 if the *project* is not implemented or is implemented poorly, partially or late, the *Commission* may reduce the grant initially provided for in line with the actual implementation of the *project* on the terms laid down in this *grant agreement*.

II.19. Interest yielded by pre-financing provided by the *Commission*

1. *Pre-financing* remains the property of the *Community* until the final payment.

2. The *Commission* shall recover from the *coordinator*, for each reporting period following the implementation of the agreement, the amount of interest generated when such pre-financing exceeds the amount fixed in the *Financial Regulation* and its *Implementing Rules*.

SECTION 2 – GUARANTEE FUND AND RECOVERIES

II.20. Guarantee Fund

1. The financial responsibility of each *beneficiary* shall be limited to its own debt, subject to the following paragraphs.

2. In accordance with Article 6, b*eneficiaries* shall contribute to the Guarantee Fund (hereinafter *the Fund*) established in order to manage the risk associated with non-recovery of sums due to the *Community* by *beneficiaries* of *grant agreements* under FP7. That contribution to be transferred by the *Commission* on their behalf may not be offset against any pending debt they may have towards the *Community*.

3. *The Fund* is the property of the *beneficiaries* of on-going *grant agreements* under FP7. The Community represented by the *Commission* shall manage it, as executive agent, on their behalf. *The Fund* shall be deposited in a bank (hereinafter *the Bank*) chosen by the *Community* represented by the *Commission*, in its quality of executive agent.

4. Interest generated by *the Fund* shall be added to it and shall be used by the *Commission* for transfers from or recoveries from the Fund referred to in paragraphs 1 and 2 of Article II.21 (hereinafter *the Operations*).

   Operations may be undertaken from the day of entry into force of the first *grant agreement* under FP7 until the day of the final payment of the last one. At the end of that period, any remaining interest shall become the property of the *Community*.

   Where interest is insufficient to cover *Operations*, contributions to *the Fund* may be used within a limit not exceeding 1% of the *Community financial contribution* due to *beneficiaries* other than those referred to in paragraph 5, at the end of the period referred to in the above paragraph. Beyond these limits or after that period, the *Commission* shall recover directly from *beneficiaries* any amount owed.

5. At the final payment made after the end of the *project*, the amount contributed to *the Fund* under this *grant agreement* shall be returned to the *beneficiaries* via the *coordinator*.

   The amount to be returned shall be equal to:

   "contribution to *the Fund under this grant agreement*" x "*Fund index*"

   The "*Fund index*" is established at the end of each month by *the Bank* to be applied during the following month, and shall equal the following ratio reduced to 1 when superior:

   ***Fund index* = (C + I + B)/C**

   where:

   C= contributions to *the Fund* of all on-going *projects* when establishing the index

   I = cumulated interest generated by *the Fund* since the start of the period

   B= (recoveries to the profit of *the Fund*) - (transfers from & recoveries on the *Fund*)

   Where, following this calculation, the amount to be returned to the *beneficiaries* is lower than the amount contributed to *the Fund* under this *grant agreement*, that deduction shall not exceed 1% of the *Community financial contribution* and shall not apply to amounts due to *public bodies* or legal entities whose participation in the *grant agreement* is guaranteed by a Member State or an *Associated country*, and higher and secondary education establishments.

   Each *beneficiary* hereby accepts that the amount to be returned to it, is assigned to the payment of any debt due by the said *beneficiary* to the *Community* under this *grant agreement* or under any other obligation irrespective of its origin, without any further formality.

II.21. Reimbursement and recoveries

1. Where, following a written request from the *Commission*, a *beneficiary* in an on-going *grant agreement* under the FP7 does not reimburse to the *coordinator* any requested amount at the latest 30 days after receipt of the request, and where the remaining *beneficiaries* agree to implement the said *grant agreement* identically regarding its objectives, the *Commission* shall order *the Bank* to directly transfer from *the Fund* an equivalent amount to the

coordinator. Amounts transferred from *the Fund* shall substitute the *Community financial contribution* not reimbursed by the *beneficiary.*

Where an amount due to the *Community* by a *beneficiary* is to be recovered after termination or completion of any *grant agreement* under the FP7, the *Commission* shall request, by means of a recovery order issued against the *beneficiary* concerned, the reimbursement of the amount due. If payment has not been made by the due date, sums owed to the *Community* may be recovered by offsetting them against any sums it owes to the *beneficiary* concerned, after informing the latter accordingly. In exceptional circumstances, justified by the necessity to safeguard the financial interests of the *Communities*, the *Commission* may recover by offsetting before the due date of the payment. The *beneficiary*'s prior consent shall not be required. Where offsetting is not possible, the *Commission* shall recover effectively from *the Fund* the amounts due.

2. Where an amount due by a *beneficiary* has been transferred or recovered from *the Fund* according to paragraphs 1 and 2, the said *beneficiary* shall reimburse that amount to *the Fund*. For this purpose, the *Commission* shall issue against that beneficiary a recovery order to the benefit of *the Fund.*

3. Each *beneficiary* hereby accepts that:

   - any pending payment excluding *pre-financing* due by the *Community* to the said *beneficiary*, irrespective of its origin, is assigned to the payment of that *beneficiary*'s debt towards the *Fund*;

   - the *Commission* may adopt a recovery decision in accordance with paragraph 5.

4. B*eneficiaries* understand that under Article 256 of the Treaty establishing the European Community, Articles 164 and 192 of the Treaty establishing the European Atomic Energy Community and as provided by the *Financial Regulation*, the *Commission* may adopt an enforceable decision formally establishing an amount as receivable from persons other than States.

5. If the obligation to pay the amount due is not honoured by the date set by the *Commission*, the sum due shall bear interest at the rate indicated in Article II.5. Interest on late payment shall cover the period between the date set for payment, exclusive and the date on which the *Commission* receives full payment of the amount owed is reimbursed in full, inclusive. Any partial payment shall first be entered against charges and interest on late payment and then against the principal.

SECTION 3 – CONTROLS AND SANCTIONS

II.22. Financial audits and controls

1. The *Commission* may, at any time during the implementation of the *project* and up to five years after the end of the *project*, arrange for financial audits to be carried out, by external auditors, or by the *Commission* services themselves including OLAF. The audit procedure shall be deemed to be initiated on the date of receipt of the relevant letter sent by the *Commission.* Such audits may cover financial, systemic and other aspects (such as accounting and management principles) relating to the proper execution of the *grant agreement.* They shall be carried out on a confidential basis.

2. The *beneficiaries* shall make available directly to the *Commission* all detailed information and data that may be requested by the *Commission* or any representative authorised by it, with a view to verifying that the *grant agreement* is properly managed and performed in accordance with its provisions and that costs have been charged in compliance with it. This information and data must be precise, complete and effective.

3. The *beneficiaries* shall keep the originals or, in exceptional cases, duly authenticated copies – including electronic copies - of all documents relating to the *grant agreement* for up to five years from the end of the *project*. These shall be made available to the *Commission* where requested during any audit under the *grant agreement*.

4. In order to carry out these audits, the *beneficiaries* shall ensure that the *Commission*'s services and any external body(ies) authorised by it have on-the-spot access at all reasonable times, notably to the *beneficiary's* offices, to its computer data, to its accounting data and to all the information needed to carry out those audits, including information on individual salaries of persons involved in the *project*. They shall ensure that the information is readily available on the spot at the moment of the audit and, if so requested, that data be handed over in an appropriate form.

5. On the basis of the findings made during the financial audit, a provisional report shall be drawn up. It shall be sent by the *Commission* or its authorised representative to the *beneficiary* concerned, which may make observations thereon within one month of receiving it. The *Commission* may decide not to take into account observations conveyed or documents sent after that deadline. The final report shall be sent to the *beneficiary* concerned within two months of expiry of the aforesaid deadline.

6. On the basis of the conclusions of the audit, the *Commission* shall take all appropriate measures which it considers necessary, including the issuing of recovery orders regarding all or part of the payments made by it and the application of any applicable sanction.

7. The European Court of Auditors shall have the same rights as the *Commission*, notably right of access, for the purpose of checks and audits, without prejudice to its own rules.

8. In addition, the *Commission* may carry out on-the-spot checks and inspections in accordance with Council Regulation (Euratom, EC) No 2185/96 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[8] and Regulation (EC) No 1073/1999 of the European Parliament and of the Council of 25 May 1999 concerning investigations conducted by the European Anti-Fraud Office (OLAF)[9] Council Regulation (Euratom) No 1074/1999 of 25 May 1999 concerning investigations conducted by the European Anti-Fraud Office (OLAF)[10].

8 OJ L 292, 15.11.1996, p.2.

9 OJ L 136, 31.5.1999

10 OJ L 136, 31.5.1999

II.23. Technical audits and reviews

1. The *Commission* may initiate a technical audit or review at any time during the implementation of the *project* and up to up to five years after the end of the *project*. The aim of a technical audit or review shall be to assess the work carried out under the *project* over a certain period, *inter alia* by evaluating the *project* reports and deliverables relevant to the period in question. Such audits and reviews may cover scientific, technological and other aspects relating to the proper execution of the *project* and the *grant agreement*.

2. With respect to the Description of Work (Annex I), the audit or review shall objectively assess the following:

   - the degree of fulfilment of the *project* work plan for the relevant period and of the related deliverables;
   - the continued relevance of the objectives and breakthrough potential with respect to the scientific and industrial state of the art;
   - the resources planned and utilised in relation to the achieved progress, in a manner consistent with the principles of economy, efficiency and effectiveness;
   - the management procedures and methods of the *project;*
   - the *beneficiaries*' contributions and integration within the *project;*
   - the expected potential impact in economic, competition and social terms, and the *beneficiaries*' plan for the *use* and *dissemination* of *foreground*.

3. Audits and reviews shall be deemed to be initiated on the date of receipt by the *beneficiary(ies)* of the relevant letter sent by the *Commission*.

4. Any such audit or review shall be carried out on a confidential basis.

5. The *Commission* may be assisted in technical audits and reviews by external scientific or technological experts. Prior to the carrying out of the evaluation task, the *Commission* shall communicate to the *beneficiaries* the identity of the appointed experts. The *beneficiary(ies)* shall have the right to refuse the participation of a particular external scientific or technological expert on grounds of commercial confidentiality.

6. Audits and reviews may be carried out remotely at the expert's home or place of work or involve sessions with *project* representatives either at the *Commission* premises or at the premises of *beneficiaries*. The *Commission* or the external scientific or technological expert may have access to the locations and premises where the work is being carried out, and to any document concerning the work.

7. The *beneficiaries* shall make available directly to the *Commission* all detailed information and data that may be requested by it or the external scientific or technological expert with a view to verifying that the *project* is being/has been properly implemented and performed in accordance with the provisions of this *grant agreement*.

8. A report on the outcome of the audits and reviews shall be drawn up. It shall be sent by the *Commission* to the *beneficiary* concerned, who may make observations thereon within one month of receiving it. The *Commission* may decide not to take into account the observations conveyed after that deadline.

9. On the basis of the experts' formal recommendations the *Commission* will inform the *coordinator* of its decision:

   - to accept or reject the deliverables;

- to allow the *project* to continue without modification of Annex I or with minor modifications;

- to consider that the *project* can only continue with major modifications;

- to initiate the termination of the *grant agreement* or of the participation of any *beneficiary* according to Article II. 38;

- to issue a recovery order regarding all or part of the payments made by the Commission and to apply any applicable sanction.

10. An ethics audit may be undertaken at the discretion of the *Commission* services up to five years after the end of the *project*. Paragraphs 3, 4, 5, 6, 7, 8 and 9 shall apply *mutatis mutandis*.

II.24. Liquidated damages

1. A *beneficiary* that is found to have overstated any amount and which has therefore received an unjustified financial contribution from the *Community* shall, without prejudice to any other measures provided for in this *grant agreement*, be liable to pay damages, hereinafter "*liquidated damages*". *Liquidated damages* are due in addition to the recovery of the unjustified *Community financial contribution* from the *beneficiary*. In exceptional cases the *Commission* may refrain from claiming *liquidated damages*.

2. Any amount of *liquidated damages* shall be proportionate to the overstated amount and the unjustified part of the *Community financial contribution*. The following formula shall be used to calculate *liquidated damages*:

   ***Liquidated damages* = unjustified *Community financial contribution* x (overstated amount/total *Community financial contribution* claimed)**

   The calculation of any *liquidated damages* shall only take into consideration the reporting period(s) relating to the *beneficiary*'s claim for the *Community financial contribution* for that period. It shall not be calculated in relation to the entire *Community financial contribution*.

3. The *Commission* shall inform the *beneficiary* which it considers liable to pay *liquidated damages* in writing of its claim by way of a registered letter with acknowledgement of receipt. The *beneficiary* shall have a period of 30 days to answer the *Community*'s claim.

4. The procedure for repayment of unjustified *Community financial contribution* and for payment of *liquidated damages* will be determined in accordance with the provisions of Article II.21. *Liquidated damages* will be deducted from any further payment or will be subject to recovery by the *Commission*.

5. The *Commission* shall be entitled to *liquidated damages* in respect of any overstated amount which comes to light after the end of the *project*, in accordance with the provisions of paragraphs 1 to 4.

II.25. Financial penalties

1. A *beneficiary* that has been guilty of making false declarations or has been found to have seriously failed to meet its obligations under this *grant agreement* shall be liable to

financial penalties of between 2% and 10% of the value of the *Community financial contribution* received by that *beneficiary*. The rate may be increased to between 4% and 20% in the event of a repeated offence within five years following the first infringement.

2. In the cases of paragraph 1, *beneficiaries* shall be excluded from all *Community* grants for a maximum of two years from the date the infringement has been established.

3. The provisions in this Article shall be without prejudice to any administrative or financial sanction that may be imposed on any defaulting *beneficiary* in accordance with the *Financial Regulation* or to any other civil remedy to which the *Community* or any other *beneficiary* may be entitled. Furthermore, these provisions shall not preclude any criminal proceedings which may be initiated by the Member States' authorities.

Part C INTELLECTUAL PROPERTY RIGHTS, *USE* AND *DISSEMINATION*

SECTION 1 – FOREGROUND

II.26. Ownership

1. *Foreground* shall be the property of the *beneficiary* carrying out the work generating that *foreground*.

2. Where several *beneficiaries* have jointly carried out work generating *foreground* and where their respective share of the work cannot be ascertained, they shall have joint ownership of such *foreground*. They shall establish an agreement[11] regarding the allocation and terms of exercising that joint ownership.

   However, where no joint ownership agreement has yet been concluded, each of the joint owners shall be entitled to grant non-exclusive licences to third parties, without any right to sub-licence, subject to the following conditions:

   a) at least 45 days prior notice must be given to the other joint owner(s); and

   b) fair and reasonable compensation must be provided to the other joint owner(s).

3. If employees or other personnel working for a *beneficiary* are entitled to claim rights to *foreground*, the *beneficiary* shall ensure that it is possible to exercise those rights in a manner compatible with its obligations under this *grant agreement*.

II.27. Transfer

1. Where a *beneficiary* transfers ownership of *foreground*, it shall pass on its obligations regarding that *foreground* to the assignee including the obligation to pass those obligations on to any subsequent assignee.

2. Subject to its obligations concerning confidentiality such as in the framework of a merger or an acquisition of an important part of its assets, where a *beneficiary* is required to pass on its

[11] The joint owners may of course agree not to continue with joint ownership but decide on an alternative regime (for example, a single owner with access rights for the other *beneficiaries* that transferred their ownership share).

obligations to provide *access rights*, it shall give at least 45 days prior notice to the other *beneficiaries* of the envisaged transfer, together with sufficient information concerning the envisaged new owner of the *foreground* to permit the other beneficiaries to exercise their *access rights*.

However, the *beneficiaries* may, by written agreement, agree on a different time-limit or waive their right to prior notice in the case of transfers of ownership from one *beneficiary* to a specifically identified third party.

3. Following notification in accordance with paragraph 2, any other *beneficiary* may object within 30 days of the notification or within a different time-limit agreed in writing, to any envisaged transfer of ownership on the grounds that it would adversely affect its *access rights*.

Where any of the other *beneficiaries* demonstrate that their *access rights* would be adversely affected, the intended transfer shall not take place until agreement has been reached between the *beneficiaries* concerned.

4. Where a *beneficiary* intends to transfer ownership of *foreground* to a third party established in a *third country* not associated to the Seventh Framework Programme, the *Commission* may object to such transfer of ownership of *foreground*, if it considers that this is not in accordance with the interests of developing the competitiveness of the European economy or is inconsistent with ethical principles or security considerations.

In such cases, the transfer of ownership shall not take place unless the *Commission* is satisfied that appropriate safeguards will be put in place and has authorised the transfer in writing.

In *projects* funded by the European Atomic Energy Community, security considerations must be understood as being the defence interests of the Member States within the meaning of Article 24 of the Treaty establishing the European Atomic Energy Community.

II.28. Protection

1. Where *foreground* is capable of industrial or commercial application, its owner shall provide for its adequate and effective protection, having due regard to its legitimate interests and the legitimate interests, particularly the commercial interests, of the other *beneficiaries*.

Where a *beneficiary* which is not the owner of the *foreground* invokes its legitimate interest, it must, in any given instance, show that it would suffer disproportionately great harm.

2. Patent applications relating to *foreground*, filed by or on behalf of a *beneficiary* must include the following statement to indicate that said *foreground* was generated with the assistance of financial support from the *Community*:

The work leading to this invention has received funding from the [European Community's] [European Atomic Energy Community's] Seventh Framework Programme ([*FP7/2007-2013*] [*FP7/2007-2011*]) under *grant agreement* n° [*xxxxxx*].[12]

[12] This statement will have to be translated into the language of the patent filing. Translations in all *Community* languages will be provided.

Furthermore, all patent applications relating to *foreground* filed shall be reported in the plan for the *use* and *dissemination* of *foreground*, including sufficient details/references to enable the *Commission* to trace the patent (application). Any such filing arising after the final report must be notified to the *Commission* including the same details/references.

3. Where the *foreground* is capable of industrial or commercial application and its owner does not protect it and does not transfer it to another *beneficiary*, an *affiliated entity* established in a Member State or *Associated country* or any other third party established in a Member State or *Associated country* along with the associated obligations in accordance with Article II.27, no *dissemination* activities relating to that *foreground* may take place before the *Commission* has been informed. The *Commission* must be informed at the latest 45 days prior to the intended *dissemination* activity.

   In such cases, the *Community* may, with the consent of the *beneficiary* concerned, assume ownership of that *foreground* and adopt measures for its adequate and effective protection. The *beneficiary* concerned may refuse consent only if it can demonstrate that its legitimate interests would suffer disproportionately great harm.

   In the event the *Community* assumes ownership, it shall take on the obligations regarding the granting of *access rights*.

II.29. *Use*

1. The *beneficiaries* shall *use* the *foreground* which they own or ensure that it is used.

2. The *beneficiaries* shall report on the expected *use* to be made of *foreground* in the plan for the *use* and *dissemination* of *foreground*. The information must be sufficiently detailed to permit the *Commission* to carry out any related audit.

II.30. *Dissemination*

1. Each *beneficiary* shall ensure that the *foreground* of which it has ownership is disseminated as swiftly as possible. If it fails to do so, the *Commission* may disseminate that *foreground*.

2. *Dissemination* activities shall be compatible with the protection of intellectual property rights, confidentiality obligations and the legitimate interests of the owner(s) of the *foreground*.

   In *projects* funded by the European Atomic Energy Community, *dissemination* activities shall also be compatible with the defence interests of the Member States within the meaning of Article 24 of the Treaty establishing the European Atomic Energy Community.

3. At least 45 days prior notice of any *dissemination* activity shall be given to the other *beneficiaries* concerned, including sufficient information concerning the planned *dissemination* activity and the data envisaged to be disseminated.

   Following notification, any of those *beneficiaries* may object within 30 days of the notification to the envisaged *dissemination* activity if it considers that its legitimate interests in relation to its *foreground* or *background* could suffer disproportionately great harm. In such cases, the *dissemination* activity may not take place unless appropriate steps are taken to safeguard these legitimate interests.

The *beneficiaries* may agree in writing on different time-limits to those set out in this paragraph, which may include a deadline for determining the appropriate steps to be taken.

4. All publications or any other *dissemination* relating to *foreground* shall include the following statement to indicate that said *foreground* was generated with the assistance of financial support from the *Community*:

The research leading to these results has received funding from the [European Community's] [European Atomic Energy Community's] Seventh Framework Programme ([*FP7/2007-2013*] [*FP7/2007-2011*]) under *grant agreement* n° [*xxxxxx*]. [13]

Any *dissemination* activity shall be reported in the plan for the *use* and *dissemination* of *foreground*, including sufficient details/references to enable the *Commission* to trace the activity. With regard to scientific publications relating to *foreground* published before or after the final report, such details/references and an abstract of the publication must be provided to the *Commission* at the latest two months following publication. Furthermore, an electronic copy of the published version or the final manuscript accepted for publication shall also be provided to the *Commission* at the same time for the purpose set out in Article II.12.2 if this does not infringe any rights of third parties.

SECTION 2 – ACCESS RIGHTS

II.31. *Background* covered

Beneficiaries may define the *background* needed for the purposes of the *project* in a written agreement and, where appropriate, may agree to exclude specific *background*[14].

II.32. Principles

1. All requests for *access rights* shall be made in writing.

2. The granting of *access rights* may be made conditional on the acceptance of specific conditions aimed at ensuring that these rights will be used only for the intended purpose and that appropriate confidentiality obligations are in place.

3. Without prejudice to their obligations regarding the granting of *access rights*, *beneficiaries* shall inform each other as soon as possible of any limitation to the granting of *access rights* to *background*, or of any other restriction which might substantially affect the granting of *access rights*.

4. The termination of the participation of a *beneficiary* shall in no way affect the obligation of that *beneficiary* to grant *access rights* to the remaining *beneficiaries*.

5. Unless otherwise agreed by the owner of the *foreground* or *background*, *access rights* shall confer no entitlement to grant sub-licences.

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[13] This statement will have to be translated into the language of the dissemination activity. Translations in all *Community* languages will be provided.

[14] Such an exclusion may be temporary (e.g. to permit the adequate protection of the *background* prior to providing access) or limited (e.g. to exclude only one or more specific *beneficiaries*). As *background* is by definition considered to be needed for implementation or use, the impact of such an exclusion on the *project*, particularly regarding an exclusion which does not have a temporary character, should be examined by the *beneficiaries*.

6. Without prejudice to paragraph 7, any agreement providing *access rights* to *foreground* or *background* to *beneficiaries* or third parties must ensure that potential *access rights* for other *beneficiaries* are maintained.

7. Exclusive licences for specific *foreground* or *background* may be granted subject to written confirmation by all the other *beneficiaries* that they waive their *access rights* thereto.

8. However, where a *beneficiary* intends to grant an exclusive licence to *foreground* to a third party established in a *third country* not associated to the Seventh Framework Programme, the *Commission* may object to the granting of such an exclusive licence, if it considers that this is not in accordance with the interests of developing the competitiveness of the European economy or is inconsistent with ethical principles or security considerations.

   In such cases, the exclusive licence shall not take place unless the *Commission* is satisfied that appropriate safeguards will be put in place and has authorised the grant in writing.

   In *projects* funded by the European Atomic Energy Community, the *Commission* may also object to the intended grant of any non-exclusive licence to a third party established in a *third country* not associated to the Seventh Framework Programme on the same conditions as set out in this paragraph. Security considerations shall in case of such *projects* be understood as being the defence interests of the Member States within the meaning of Article 24 of the Treaty establishing the European Atomic Energy Community.

II.33. *Access rights* for implementation

1. *Access rights* to *foreground* shall be granted to the other *beneficiaries*, if it is needed to enable those *beneficiaries* to carry out their own work under the *project*.

   Such *access rights* shall be granted on a royalty-free basis.

2. *Access rights* to *background* shall be granted to the other *beneficiaries*, if it is needed to enable those *beneficiaries* to carry out their own work under the *project* provided that the *beneficiary* concerned is entitled to grant them.

   Such *access rights* shall be granted on a royalty-free basis, unless otherwise agreed by all *beneficiaries* before their accession to this agreement.

II.34. *Access rights* for *use*

1. *Beneficiaries* shall enjoy *access rights* to *foreground*, if it is needed to use their own *foreground*.

   Subject to agreement, such *access rights* shall be granted either under *fair and reasonable conditions* or be royalty-free.

2. *Beneficiaries* shall enjoy *access rights* to *background*, if it is needed to use their own *foreground* provided that the *beneficiary* concerned is entitled to grant them.

   Subject to agreement, such *access rights* shall be granted either under *fair and reasonable conditions* or be royalty-free.

3. An *affiliated entity* established in a Member State or *Associated country* shall also enjoy *access rights*, referred to in paragraphs 1 and 2, to *foreground* or *background* under the

same conditions as the *beneficiary* to which it is affiliated, unless otherwise provided for in the *consortium agreement*. As the *access rights* referred to in paragraphs 1 and 2 require that access is needed to use own *foreground*, this paragraph only applies to the extent that ownership of *foreground* was transferred to an affiliate entity established in a Member State or *Associated country*. The *beneficiaries* may provide for arrangements regarding *access rights* for affiliated entities in their *consortium agreement*, including regarding any notification requirements.

4. A request for *access rights* under paragraphs 1, 2 or 3 may be made up to one year after either of the following events:

   a) the end of the *project*; or

   b) termination of participation by the owner of the *background* or *foreground* concerned.

   However, the *beneficiaries* concerned may agree on a different time-limit[15].

FINAL PROVISIONS

II.35. Competitive calls

1. When required by the terms of Annex I, the *consortium* shall identify and propose to the *Commission* the participation of new *beneficiaries* following a competitive call in accordance with the provisions of this Article.

2. The *consortium* shall publish the competitive call at least in one international journal and in three different national newspapers in three different Member States or *Associated countries*. It shall also be responsible for advertising the call widely using specific information support, particularly Internet sites on the Seventh Framework Programme, the specialist press and brochures and through the national contact points set up by Member States and *Associated countries*. In addition, the publication and advertising of the call shall conform to any instructions and guidance notes established by the *Commission*. The *consortium* shall inform the *Commission* of the call and its content at least 30 days prior to its expected date of publication.

3. The competitive call shall remain open for the submission of proposals by interested parties for a period of at least five weeks.

4. The *consortium* shall evaluate offers received in the light of the criteria that governed the *Commission*'s evaluation and selection of the *project*, defined in the relevant call for proposals, and with the assistance of at least two independent experts appointed by the *consortium* on the basis of the criteria described in the *Rules for Participation*.

5. The *consortium* shall notify the *Commission* of the proposed accession of a new *beneficiary(ies)* in accordance with Article II.36. At the same time, it will inform the *Commission* of the means by which the competitive call was published and of the names and affiliation of the experts involved in the evaluation. The *Commission* may object to the accession of any new *beneficiary* within 45 days of the receipt of the notification.

[15] This can be a longer or shorter time-limit.

II.36. Requests for amendments and termination at the initiative of the *consortium*

1. Amendments to this *grant agreement* may be requested by any of the parties. Requests for amendments and termination shall be signed by the legal representative of the parties and submitted in accordance with Article 8. Any request or acceptance by the *consortium* or a *beneficiary*(ies) shall be submitted by the *coordinator*. The *coordinator* is deemed to act on behalf of all *beneficiaries* when signing a request, an acceptance or rejection letter concerning an amendment as well as when requesting a termination. The *coordinator* shall ensure that adequate proof of the *consortium's* agreement to such an amendment or termination exists and is made available in the event of an audit or upon request of the *Commission*.

2. In the case of change of *coordinator* without its agreement, the request shall be submitted by all other *beneficiaries* or by one of them representing the others.

3. A request for amendment including more than one modification to the agreement shall be considered a package that cannot be separated into several requests and shall be approved or rejected by the other party as a whole, except where the request explicitly states that it contains separate requests that can be approved independently.

4. Requests for the addition of a new *beneficiary* shall include a completed Form B (Annex V), duly signed by such new entity. Any addition is subject to the conditions required by the *Rules for Participation*, the related call for proposals and the *Financial Regulation.* Such additional entity shall assume the rights and obligations of *beneficiaries* as established by the *grant agreement* with effect from the date of its accession specified in the signed Form B.

5. The amendments may not have the purpose or the effect of making changes to the agreement which might call into question the decision awarding the grant or result in unequal treatment of the *beneficiaries.*

6. Requests for termination of the participation of one or more *beneficiaries* shall include:

   - the *consortium's* proposal for reallocation of the tasks and budget of that *beneficiary*,
   - the reasons for requesting the termination,
   - the proposed date on which the termination shall take effect,
   - a letter containing the opinion of the *beneficiary* whose participation is requested to be terminated and
   - the reports and deliverables referred to in Article II.4, relating to the work carried out by this *beneficiary* up to the date on which the termination takes effect, together with a comment of the *coordinator* on behalf of the *consortium* on these reports and deliverables and a declaration on distribution of payments to this *beneficiary* by the *coordinator*.

   In the absence of receipt of such documents, the request shall not be considered as a valid request.

The letter containing the opinion of the *beneficiary* concerned can be substituted by proof that this *beneficiary* has been requested in writing to express its opinion on the proposed termination of its participation and to send the reports and deliverables but failed to do so within the time-limit established by that notification. This time-limit shall not be inferior to one month. In this case, if no reports have been submitted with the request for termination, the *Commission* shall not take into account any further cost claims of that *beneficiary* and shall not make any further reimbursement for it.

Unless otherwise agreed with the *Commission*, all the tasks of the *beneficiary* whose participation is terminated must be reallocated within the *consortium*.

Requests for termination of the *grant agreements* shall provide the justification for termination and the reports and deliverables referred to in Article II.4 relating to the work carried out up to the date on which the termination takes effect.

II.37. Approval of amendments and termination requested by the *consortium*

1. The parties to this *grant agreement* undertake to approve or reject any valid request for an amendment or termination within 45 days of its receipt. The absence of a response within 45 days of receipt of such a request shall be considered as a rejection.

2. By derogation to paragraph 1, when the *consortium* requests the addition or the termination of the participation of a *beneficiary*, the absence of a response from the *Commission* within 45 days of receipt of such a request constitutes approval, except in cases of absence of the agreement of the *beneficiary* concerned and in cases of appointment of a new *coordinator,* which shall require the written approval of the *Commission*.

   Where the *Commission* does not object within this period, it is deemed to have approved the request on the last day of the time-limit. The *Commission* undertakes to send a letter for information purposes in case of tacit approval.

   Where the request for the addition or removal of a *beneficiary* is associated with requests for other modifications to the *grant agreement* which are not directly related to this addition or removal, the whole request shall be subject to written approval by the *Commission*.

3. The *Commission*'s approval of the requested amendment or termination shall be notified to the *coordinator*, which receives it on behalf of the *consortium*. In case of termination of the participation of one or more *beneficiaries*, the *Commission* shall send a copy to the *beneficiary* concerned.

4. Amendments and terminations shall take effect on the date agreed by the parties; where there is no date specified they shall take effect on the date of the *Commission*'s approval.

II.38. Termination of the *grant agreement* or of the participation of one or more *beneficiaries* at the *Commission*'s initiative

1. The *Commission* may terminate the *grant agreement* or the participation of a *beneficiary* in the following cases:

   a) where one or more of the legal entities identified in Article 1 does not accede to this *grant agreement*.

b) in case of non-performance or poor performance of the work or breach of any substantial obligation imposed by this *grant agreement* that is not remedied following a written request to the *consortium* to rectify the situation within a period of 30 days;

c) where the *beneficiary* has deliberately or through negligence committed an *irregularity* in the performance of any *grant agreement* with the *Commission*;

d) where the *beneficiary* has contravened fundamental ethical principles;

e) where the required reports or deliverables are not submitted or the *Commission* does not approve the reports or deliverables submitted;

f) for major technical or economic reasons substantially adversely affecting the completion of the *project*;

g) if the potential *use* of the *foreground* diminishes to a considerable extent;

h) where a legal, financial, organisational or technical change or *change of control* of a *beneficiary* calls into question the decision of the *Commission* to accept its participation;

i) where any such change identified in h) above or termination of the participation of the *beneficiary(ies)* concerned substantially affects the implementation of the *project*, or the interests of the *Community*, or calls into question the decision to grant the *Community* contribution;

j) in case of *force majeure* notified in conformity with Article II.40, where any reactivation of the *project* after suspension is impossible;

k) where the conditions for participation in the *project* established by the *Rules for Participation* or as amended by the call for proposals to which the *project* was submitted are no longer satisfied, unless the *Commission* considers that the continuation of the *project* is essential to the implementation of the specific programme;

l) where a *beneficiary* is found guilty of an offence involving its professional conduct by a judgment having the force of *res judicata* or if it is guilty of grave professional misconduct proven by any justified means;

m) where further to the termination of the participation of one or more *beneficiaries*, the *consortium* does not propose to the *Commission* an amendment to the *grant agreement* with the necessary modifications for the continuation of the *project* including the reallocation of task of the *beneficiary* whose participation is terminated within the time-limit determined by the *Commission*, or where the *Commission* does not accept the proposed modifications.

n) where a *beneficiary* is declared bankrupt or is being wound up.

2. Termination of the participation of one or more *beneficiaries* at the *Commission's* initiative shall be notified to the *beneficiary(ies)* concerned, with a copy to the *coordinator* and shall take effect on the date indicated in the notification and at the latest 30 days after its receipt by the *beneficiary*.

The *Commission* shall inform the *consortium* of the effective date of termination.

In the case of termination of the *grant agreement*, the *coordinator* shall be notified, who shall in turn notify all the other *beneficiaries* and the termination shall become effective 45 days after receipt by the *coordinator*.

3. Within 45 days after the effective date of termination, the *beneficiary(ies)* whose participation is terminated shall submit (through the *coordinato*r) all required reports and deliverables referred to in Article II.4 relating to the work carried out up to that date. In the absence of receipt of such documents within the above time-limits, the *Commission* may, after providing 30 days notice in writing of the non-receipt of such documents, determine not to take into account any further cost claims and not to make any further reimbursement and, where appropriate, require the reimbursement of any *pre-financing* due by the *beneficiary(ies).*

4. The *consortium* has up to 30 days after the effective date of termination of the *beneficiary*'s participation to provide the *Commission* with information on the share of the *Community* contribution that has been effectively transferred to such *beneficiary* since the beginning of the *project*.

5. In the absence of receipt of such information within the time-limits, the *Commission* shall consider that the *beneficiary* whose participation is terminated owes no money to the *Commission* and that the *Community* contribution already paid is still at the disposal of the *consortium* and under its responsibility.

6. Based on documents and information referred to in the paragraphs above, the *Commission* shall establish the debt owed by the *beneficiary* whose participation is terminated.

7. Where the participation of one or more *beneficiaries* is terminated, the *beneficiary(ies)* whose participation is terminated shall reimburse the amount due to the *Commission* or transfer it to the *coordinator* as requested by the *Commission*, within 30 days. The Commission shall send a copy of such a request to the *coordinator*. In the latter case, the *coordinator* shall inform the *Commission* at the latest 10 days after the end of this time-limit whether the amount has been transferred to it.

8. Where the *grant agreement* is terminated, the *Commission* shall establish the debt owed by the *consortium* and notify it to the *coordinator*.

II.39. Financial contribution after termination and other termination consequences

1. In the event of termination any financial contribution from the *Community* is limited to those *eligible costs* incurred and accepted up to the effective date of such termination and of any legitimate commitments taken prior to that date, which cannot be cancelled.

2. By derogation to the above paragraph:

   - in the case of Article II.38.1.a), no costs incurred by the *consortium* under the *project* can be approved or accepted as eligible for reimbursement by the *Community*. Any *pre-financing* provided to the *consortium* and any interest generated by the *pre-financing* must be returned in full to the *Commission.*

   - in the case of Article II.38.1.b), any financial contribution from the *Community* is limited to those eligible costs incurred up to the date of receipt of the written request to rectify the breach.

3. In addition, in the cases of Article II.38.1.b), c), d), e), l) and m) the *Commission* may require reimbursement of all or part of the *Community's* financial contribution. In the case of Article II.38.1.b) and m) the *Commission* shall take into account the nature and results of the work carried out and its usefulness to the *Community* in the context of the specific programme concerned.

4. Reports and deliverables submitted in the framework of a termination are deemed to be submitted at the end of the corresponding reporting period.

5. Where the *Community* makes a payment after the termination of the participation of a *beneficiary* or after termination of the *grant agreement*, this payment shall be considered as a final payment in relation to such *beneficiary(ies)* or the *project*, respectively and in any case shall be done through the *coordinator*.

Notwithstanding the termination of the *grant agreement* or the participation of one or more *beneficiaries*, the provisions identified in Articles II.9, II.10, II.11, II.12, II.21, II.22, II.23, II.24, II.25, II.35, II.36, II.38, II.41, II.42 and Part C of Annex II continue to apply after the termination of the *grant agreement* or the termination of the participation of such *beneficiary(ies).*

II.40. Force majeure

1. *Force majeure* shall mean any unforeseeable and exceptional event affecting the fulfilment of any obligation under this *grant agreement* by the parties, which is beyond their control and cannot be overcome despite their reasonable endeavours. Any default of a product or service or delays in making them available for the purpose of performing this *grant agreement* and affecting such performance, including, for instance, anomalies in the functioning or performance of such product or service, labour disputes, strikes or financial difficulties do not constitute *force majeure.*

2. If any of the *beneficiaries* is subject to *force majeure* liable to affect the fulfilment of its obligations under this *grant agreement*, the *coordinator* shall notify the *Commission* without delay, stating the nature, likely duration and foreseeable effects.

3. If the *Community* is subject to *force majeure* liable to affect the fulfilment of its obligations under this *grant agreement*, it shall notify the *coordinator* without delay, stating the nature, likely duration and foreseeable effects.

4. No party shall be considered to be in breach of its obligation to execute the *project* if it has been prevented from complying by *force majeure*. Where *beneficiaries* cannot fulfil their obligations to execute the *project* due to *force majeure*, remuneration for accepted eligible costs incurred may be made only for tasks which have actually been executed up to the date of the event identified as *force majeure*. All necessary measures shall be taken to limit damage to the minimum.

II.41. Assignment

The *beneficiaries* shall not assign any of the rights and obligations arising from the *grant agreement* except those cases provided for in Article II.27 (transfer of *foreground*), without the prior and written authorisation of the *Commission* and the other *beneficiaries*.

II.42. Liability

1. The *Community* cannot be held liable for any acts or omissions of the *beneficiaries* in relation to this *grant agreement*. It shall not be liable for any defaults of any products, processes or services created on the basis of *foreground*, including, for instance, anomalies in the functioning or performance thereof.

2. Each *beneficiary* fully guarantees the *Community*, and agrees to indemnify it, in case of any action, complaint or proceeding brought by a third party against the *Community* as a result of damage caused, either by any of its acts or omissions in relation to this *grant agreement*, or by any products, processes or services created by it on the basis of *foreground* resulting from the *project.*

   In the event of any action brought by a third party against a *beneficiary* in connection with the performance of this *grant agreement*, the *Commission* may assist the latter upon written request. The costs incurred by the *Commission* in this connection shall be borne by the *beneficiary* concerned.

3. Each *beneficiary* shall bear sole responsibility for ensuring that their acts within the framework of this *project* do not infringe third parties rights.

4. The *Community* cannot be held liable for any consequences arising from the proper exercise of the rights of the *Community* under the *Rules for Participation* or this *grant agreement*.

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

FUNDACIO IMIM, represented for the purpose hereof by Mr Andreu FORT, Manager, or his authorised representative, established in SPAIN - PASSEIG MARITIM 25-29, 08003 BARCELONA acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°2")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by FUNDACIO IMIM, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: FUNDACIO IMIM

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

UNIVERSITAT POMPEU FABRA, represented for the purpose hereof by Mr JOSEP JOAN MORESO, RECTOR, or his authorised representative, established in SPAIN - PLACA DE LA MERCE 10-12, 08002 BARCELONA acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°3")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by UNIVERSITAT POMPEU FABRA, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: UNIVERSITAT POMPEU FABRA

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

UNIVERSIDADE DE AVEIRO, represented for the purpose hereof by Mr Francisco VAZ, Vice-Rector, or his authorised representative, established in PORTUGAL - CAMPO UNIVERSITARIO DE SANTIAGO, 3800 AVEIRO acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°4")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by UNIVERSIDADE DE AVEIRO, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: UNIVERSIDADE DE AVEIRO

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

IRCCS CENTRO NEUROLESI BONINO PULEJO, represented for the purpose hereof by Mr Raffaele TOMMASINI, General Director, or his authorised representative, established in ITALY - CTR CASAZZA VIA PALERMO SS 113, 98124 MESSINA acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°5")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by IRCCS CENTRO NEUROLESI BONINO PULEJO, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: IRCCS CENTRO NEUROLESI BONINO PULEJO

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

UNIVERSITE VICTOR SEGALEN BORDEAUX II, represented for the purpose hereof by Mr Bernard BEGAUD, President de l'Université, or his authorised representative, established in FRANCE - RUE LEO SAIGNAT 146, 33076 BORDEAUX CEDEX acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°6")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by UNIVERSITE VICTOR SEGALEN BORDEAUX II, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: UNIVERSITE VICTOR SEGALEN BORDEAUX II

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, represented for the purpose hereof by Ms Penny IRELAND, Research Contracts Officer, or her authorised representative, established in UNITED KINGDOM - KEPPEL STREET, LONDON WC1E7HT acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°7")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

AARHUS UNIVERSITETSHOSPITAL, AARHUS SYGEHUS, represented for the purpose hereof by Mr Ole THOMSEN, Hospital Director and/or Ms Anne THOMASSEN, Medical Director, or their authorised representative, established in DENMARK - NORREBROGADE 44, 8000 AARHUS acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°8")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by AARHUS UNIVERSITETSHOSPITAL, AARHUS SYGEHUS, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: AARHUS UNIVERSITETSHOSPITAL, AARHUS SYGEHUS

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

ASTRAZENECA AB, represented for the purpose hereof by Mr Peter MOLDEUS, Vice President, or his authorised representative, established in SWEDEN - 151 85 SOEDERTAELJE acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°9")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by ASTRAZENECA AB, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: ASTRAZENECA AB

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

THE UNIVERSITY OF NOTTINGHAM, represented for the purpose hereof by Mr Martin WYNNE-JONES, Director of Finance, or his authorised representative, established in UNITED KINGDOM - UNIVERSITY PARK, NOTTINGHAM NG7 2RD acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°10")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by THE UNIVERSITY OF NOTTINGHAM, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: THE UNIVERSITY OF NOTTINGHAM

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

UNIVERSITA DEGLI STUDI DI MILANO - BICOCCA, represented for the purpose hereof by Mr Marcello FONTANESI, Rector, or his authorised representative, established in ITALY - PIAZZA DELL'ATENEO NUOVO 1, 20126 MILANO acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°11")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by UNIVERSITA DEGLI STUDI DI MILANO - BICOCCA, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: UNIVERSITA DEGLI STUDI DI MILANO - BICOCCA

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

AGENZIA REGIONALE DI SANITA, represented for the purpose hereof by Mr GIOVANNI BARBAGLI, PRESIDENT, or his authorised representative, established in ITALY - VIA VITTORIO EMANUELE II 64, 50134 FIRENZE acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°12")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by AGENZIA REGIONALE DI SANITA, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: AGENZIA REGIONALE DI SANITA

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

PHARMO COOPERATIE UA, represented for the purpose hereof by Mr Ernst Jan DE GRAAG, Managing Director, or his authorised representative, established in THE NETHERLANDS - PAPENDORPSEWEG 65, 3528BJ UTRECHT acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°13")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by PHARMO COOPERATIE UA, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: PHARMO COOPERATIE UA

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

SOCIETA SERVIZI TELEMATICI SRL, represented for the purpose hereof by Mr Luigi CANTARUTTI, President, or his authorised representative, established in ITALY - VIA MEDICI GIACOMO 9/A, 35138 PADOVA acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°14")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by SOCIETA SERVIZI TELEMATICI SRL, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: SOCIETA SERVIZI TELEMATICI SRL

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX IV - FORM A – ACCESSION OF BENEFICIARIES TO THE GRANT AGREEMENT

UNIVERSIDADE DE SANTIAGO DE COMPOSTELA, represented for the purpose hereof by Ms María José ALONSO FERNÁNDEZ, Vicechancellor for Research and Innovation, or her authorised representative, established in SPAIN - PRAZA DO OBRADOIRO S/N, PAZO DE SAN XEROME, 15782 SANTIAGO DE COMPOSTELA acting as its legal authorised representative, hereby consents to become a beneficiary *("beneficiary n°15")* to *grant agreement n°* 215847 (relating to *project* 'Early Detection of Adverse Drug Events by Integrative Mining of Clinical Records and Biomedical Knowledge') concluded between the Commission of the European Communities and ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM established in THE NETHERLANDS - DR. MOLEWATERPLEIN 40/50, 3015 GE ROTTERDAM and accepts in accordance with the provisions of the aforementioned *grant agreement* all the rights and obligations of a *beneficiary*.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by UNIVERSIDADE DE SANTIAGO DE COMPOSTELA, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 1.1 and 1.2 and Article 8 of the *grant agreement.*

Name of Legal Entity: UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Name of legal representative(s): (written out in full)

Signature of legal representative(s):

Date:
Stamp of the organisation

Name of Legal Entity: ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM

Name of legal representative: (written out in full)

Signature of legal representative:

Date:
Stamp of the organisation

FP7 GRANT AGREEMENT
ANNEX V - FORM B – REQUEST FOR ACCESION OF A NEW BENEFICIARY TO THE GRANT AGREEMENT

*(*to be filled in by each *new legal entity* willing to become a *beneficiary)*

[full name and legal form of new beneficiary], represented for the purpose hereof by *[(name of legal representative) (function)* [and/or *(name of legal representative), (function)], or her/his/their authorised representative established in (full address: city/state/province/country)]* acting as its legal authorised representative, hereby requests to become a *beneficiary ("beneficiary no.")* to grant agreement No …… (relating to project *[title]*) concluded between the *Commission* of the European *Communities* and *[name of the coordinator]* and accepts, in accordance with the provisions of the aforementioned *grant agreement*, all the rights and obligations of a *beneficiary* starting on [date], should the *Commission* not oppose this request within six weeks of its receipt.

[name of the coordinator and legal form (acronym) established in (full address: city/state/province/country)], represented for the purpose hereof by *[(name of legal representative), (function) [and/or (name of legal representative), (function)], or her/his/their authorised representative established in (full address: city/state/province/country)]* acting as its legal authorised representative, hereby certifies as representative of the *beneficiary* to *grant agreement* No…… (relating to *project [title]*) that the *consortium* proposes and agrees to the accession of *[full name and legal form of new beneficiary]* to the aforementioned *grant agreement* as *beneficiary* starting on the above-mentioned date.

Enclosures:

- Grant Agreement Preparation Forms duly completed and signed by the new *beneficiary*.

- modified Annex I to the *grant agreement* describing the work to be performed by the new *beneficiary*.

- where the new *beneficiary* is proposed by the *consortium* following a competitive call, documents required by the grant agreement shall be provided in addition to this Form. If a competitive call has not been carried out to select this/these *beneficiary(ies)*, justification for selection of this/these *beneficiary(ies)* and, where necessary, justification for not having used a competitive call.

Done in 3 copies, of which one shall be kept by the *coordinator* and one by [name of new *beneficiary]*, the third being sent to the *Commission* by the *coordinator* in accordance with Articles 8 and II.36 of the *Grant Agreement*

[name of the new beneficiary (legal entity)]
Name of legal representative(s): (written out in full)
Signature of legal representative(s):

Date:
Stamp of the organisation

[name of the coordinator (legal entity]
Name of legal representative: (written out in full)
Signature of legal representative:
Date:
Stamp of the organisation

FP7 - Grant Agreement - Annex VI - Collaborative Project

Summary Financial Report - Collaborative Project- to be filled in by the coordinator

Project acronym	xxxxxxxxxxxxxxxxxxxxxxxxx	Project nr	nnnnnn	Reporting period from	dd/mm/aa	to:	dd/mm/aa	Page	1/1

Funding scheme	CP

Beneficiary n°	If 3rd Party, linked to beneficiary	Adjustment (Yes/No)	Organisation Short Name	Type of activity								Total (A)+(B)+(C)+(D)		Receipts	Interest
				RTD (A)		Demonstration (B)		Management (C)		Other (D)					
				Total	Max EC Contribution	Total	Max EC Contribution	Total	Max EC Contribution	Total	Max EC Contribution	Total	Max EC Contribution		
1															
2															
3															
4															
5															
6															
7															
8															
9															
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17															
18															
19															
20															
21															
22															
23															
24															
25															
TOTAL															

Requested EC contribution for the reporting period (in €)	

FP7 - Grant Agreement - Annex VI - Collaborative Projec

Form C - Financial Statement (to be filled in by each beneficiary)

Project nr	**nnnnnn**	**Funding scheme**	**Collaborative Project**
Project Acronym	**xxxxxxxxxxxxxxxxxxxx**		
Period from	dd/mm/aa	Is this an adjustment to a previous statement ?	**Yes/No**
To	dd/mm/aa		

Legal Name		**Participant Identity Code**	**nn**
Organisation short Name		**Beneficiary nr**	**nn**

Funding % for RTD activities (A)		**If flat rate for indirect costs, specify %**	**%**

1- Declaration of eligible costs/lump sum/flate-rate/scale of unit (in€)

	Type of Activity				
	RTD (A)	**Demonstration (B)**	**Management (C)**	**Other (D)**	**TOTAL (A+B+C+D)**
Personnel costs					
Subcontracting					
Other direct costs					
Indirect costs					
Lump sums/flat-rate/scale of unit declared					
Total					
Maximum EC contribution					
Requested EC contribution					

2- Declaration of receipts

Did you receive any financial transfers or contributions in kind, free of charge from third parties or did the project generate any income which could be considered a receipt according to Art.II.17 of the grant agreement ? — Yes/No

If yes, please mention the amount (in €)

3- Declaration of interest yielded by the pre-financing(to *be completed only by the coordinator*)

Did the pre-financing you received generate any interest according to Art. II.19 ? — Yes/No

If yes, please mention the amount (in €)

4. Certificate on the methodology

Do you declare average personnel costs according to Art. II.14.1 ? — Yes/No

Is there a certificate on the methodology provided by an independent auditor and accepted by the Commission according to Art. II.4.4 ? — Yes/No

Name of the auditor		**Cost of the certificate (in€), if charged under this project**	

5- Certificate on the financial statements

Is there a certificate on the financial statements provided by an independent auditor attached to this financial statement according to Art.II.4.4 ? — Yes/No

Name of the auditor		**Cost of the certificate (in€)**	

6- Beneficiary's declaration on its honour

We declare on our honour that:

- the costs declared above are directly related to the resources used to attain the objectives of the project and fall within the definition of eligible costs specified in Articles II.14 and II.15 of the grant agreement, and, if relevant, Annex III and Article 7 (special clauses) of the grant agreement;

- the receipts declared above are the only financial transfers or contributions in kind, free of charge, from third parties and the only income generated by the project which could be considered as receipts according to Art. II.17 of the grant agreement;

- the interest declared above is the only interest yielded by the pre-financing which falls within the definition of Art. II.19 of the grant agreement ;

- there is full supporting documentation to justify the information hereby declared. It will be made available at the request of the Commission and in the event of an audit by the Commission and/or by the Court of Auditors and/or their authorised representatives.

Beneficiary's Stamp	**Name of the Person(s) Authorised to sign this Financial Statement**
	Date & signature

Form C - Financial Statement (to be filled in by Third Party) Only applicable if special clause nr 10 is used

Project nr	**nnnnnn**	**Funding scheme**	**Collaborative Project**
Project Acronym	**xxxxxxxxxxxxxxxxxxxx**		
Period from	dd/mm/aa	Is this an adjustment to a previous statement ?	**Yes/No**
To	dd/mm/aa		
3rd party legal Name			
3rd party Organisation short Name		**Working for beneficiary nr**	**nn**
Funding % for RTD activities (A)		**If flat rate for indirect costs, specify %**	**%**

1- Declaration of eligible costs/lump sum/flate-rate/scale of unit (in€)

	Type of Activity				
	RTD (A)	**Demonstration (B)**	**Management (C)**	**Other (D)**	**TOTAL (A+B+C+D)**
Personnel costs					
Subcontracting					
Other direct costs					
Indirect costs					
Lump sums/flat-rate/scale of unit declared					
Total					
Maximum EC contribution					
Requested EC contribution					

2- Declaration of receipts

Did you receive any financial transfers or contributions in kind, free of charge from third parties or did the project generate any income which could be considered a receipt according to Art.II.17 of the grant agreement ? Yes/No

If yes, please mention the amount (in €)

3- Declaration of interest yielded by the pre-financing (*to be completed only by the coordinator*)

Did the pre-financing you received generate any interest according to Art. II.19 ? Yes/No

If yes, please mention the amount (in €)

4. Certificate on the methodology

Do you declare average personnel costs according to Art. II.14.1 ? Yes/No

Is there a certificate on the methodology provided by an independent auditor and accepted by the Commission according to Art. II.4.4 ? Yes/No

Name of the auditor		**Cost of the certificate (in€), if charged under this project**	

5- Certificate on the financial statements

Is there a certificate on the financial statements provided by an independent auditor attached to this financial statement according to Art.II.4.4 ? Yes/No

Name of the auditor		**Cost of the certificate (in€)**	

6- Beneficiary's declaration on its honour

We declare on our honour that:

- the costs declared above are directly related to the resources used to attain the objectives of the project and fall within the definition of eligible costs specified in Articles II.14 and II.15 of the grant agreement, and, if relevant, Annex III and Article 7 (special clauses) of the grant agreement;

- the receipts declared above are the only financial transfers or contributions in kind, free of charge, from third parties and the only income generated by the project which could be considered as receipts according to Art. II.17 of the grant agreement;

- the interest declared above is the only interest yielded by the pre-financing which falls within the definition of Art. II.19 of the grant agreement ;

- there is full supporting documentation to justify the information hereby declared. It will be made available at the request of the Commission and in the event of an audit by the Commission and/or by the Court of Auditors and/or their authorised representatives.

Beneficiary's Stamp	**Name of the Person(s) Authorised to sign this Financial Statement**
	Date & signature

FP7 GRANT AGREEMENT –

ANNEX VII - FORM D - TERMS OF REFERENCE FOR THE CERTIFICATE OF FINANCIAL STATEMENTS

TABLE OF CONTENTS

The Terms Reference should be completed by the Beneficiary and be agreed with the Auditor

The Independent Report of Factual Findings should be provided by the Auditor

Terms of Reference for an Independent Report of Factual Findings on costs claimed under a Grant Agreement financed under the Seventh Research Framework Programme (FP7)

The following are the terms of reference ('ToR') on which <*name of the Beneficiary*> 'the Beneficiary' agrees to engage < *name of the audit firm*> 'the Auditor' to provide an independent report of factual findings on a Financial Statement(s)[1] prepared by the Beneficiary and to report in connection with a European Community/European Atomic Energy Community financed grant agreement concerning the Seventh Research Framework Programme (FP7), concerning < *title and number of the grant agreement*> (the 'Grant Agreement'). Where in these ToR the 'European Commission' is mentioned this refers to its quality as signatory of the Grant Agreement with the Beneficiary. The European Community is not a party to this engagement.

1.1 Responsibilities of the Parties to the Engagement

'**The Beneficiary'** refers to the legal entity that is receiving the grant and that has signed the Grant Agreement with the European Commission.

- The Beneficiary is responsible for preparing a Financial Statement for the Action financed by the Grant Agreement in compliance with such agreements and providing it to the Auditor, and for ensuring that this Financial Statement can be properly reconciled to the Beneficiary's accounting and bookkeeping system and to the underlying accounts and records. Notwithstanding the procedures to be carried out, the Beneficiary remains at all times responsible and reliable for the accuracy of the Financial Statement.

- The Beneficiary is responsible for the factual statements which will enable the Auditor to carry out the procedures specified, and will provide the Auditor with a written representation letter supporting these statements, clearly dated and stating the period covered by the statements.

- The Beneficiary accepts that the ability of the Auditor to perform the procedures required by this engagement effectively depends upon the Beneficiary providing full and free access to the Beneficiary's staff and its accounting and other relevant records.

'**The Auditor'** refers to the Auditor who is responsible for performing the agreed-upon procedures as specified in these ToR, and for submitting an independent report of factual findings to the Beneficiary.

The Auditor must be independent from the Beneficiary.

- [*Option 1: delete if not applicable*] The Auditor is qualified to carry out statutory audits of accounting documents in accordance with the Directive 2006/43/EC of the European Parliament and of the Council of 17 May 2006 on statutory audits of annual accounts and consolidated accounts, amending Council Directives 78/660/EEC and 83/349/EEC and repealing Council Directive 84/253/EEC or similar national regulations.

- [*Option 2: delete if not applicable*] The Auditor is a Competent Public Officer for which the relevant national authorities have established the legal capacity to audit the Beneficiary and has not been involved in the preparation of the financial statements.

- The procedures to be performed are specified by the European Commission and the Auditor is not responsible for the suitability and appropriateness of these procedures.

1.2 Subject of the Engagement

[1] Financial Statement in this context refers solely to Form C - Annex VI by which the Beneficiary claims costs under the Grant Agreement.

The subject of this engagement is the <*interim or final; delete what is not applicable*> Financial Statement in connection with the Grant Agreement for the period covering <*dd Month yyyy to dd Month yyyy*>.

1.3 Reason for the Engagement

The Beneficiary is required to submit to the European Commission a certificate on a Financial Statement in the form of an independent report of factual findings produced by an external auditor in support of the payment requested by the Beneficiary under Article II.4 of the Grant Agreement. The Authorising Officer of the Commission requires this Report as he makes the payment of costs requested by the Beneficiary conditional on the factual findings of this Report.

1.4 Engagement Type and Objective

This constitutes an engagement to perform specific agreed-upon procedures regarding an independent report of factual findings on costs claimed under the Grant Agreement.

As this engagement is not an assurance engagement the Auditor does not provide an audit opinion and expresses no assurance. The European Commission derives its assurance by drawing its own conclusions from the factual findings reported by the Auditor on the Financial Statement and the payment request of the Beneficiary relating thereto.

The Auditor shall include in its Report that no conflict of interest exists between it and the Beneficiary in establishing this Report, as well as the fee paid to the Auditor for providing the Report.

1.5 Scope of Work

1.5.1 The Auditor shall undertake this engagement in accordance with these ToR and:

- in accordance with the International Standard on Related Services ('ISRS') 4400 *Engagements to perform Agreed-upon Procedures regarding Financial Information* as promulgated by the IFAC;

- in compliance with the *Code of Ethics for Professional Accountants* issued by the IFAC. Although ISRS 4400 provides that independence is not a requirement for agreed-upon procedures engagements, the European Commission requires that the Auditor also complies with the independence requirements of the *Code of Ethics for Professional Accountants*.

1.5.2 Planning, procedures, documentation and evidence

The Auditor should plan the work so that the procedures can be effectively performed. For this purpose he performs the procedures specified in 1.9 of these Terms of Reference ('Scope of Work – Compulsory Report Format and Procedures to be Performed') and uses the evidence obtained from these procedures as the basis for the Report of factual findings.

1.6 Reporting

The Report of factual findings, an example of which is attached to this ToR, should describe the purpose and the agreed-upon procedures of the engagement in sufficient detail in order to enable the Beneficiary and the European Commission to understand the nature and extent of the procedures performed by the Auditor. Use of the reporting format attached as Annex VII of the Grant Agreement is compulsory. The Report should be written in the language indicated in Article 4 of the Grant Agreement. In accordance with Article II.22 of the Grant Agreement, the European Commission and the Court of Auditors have the right to audit any work carried out under the project for which costs are claimed from the Community, including the work related to this engagement.

1.7 Timing

The Report should be provided by [DATE].

1.8 Other Terms

[*The Beneficiary and the Auditor can use this section to agree other specific terms such as Auditor's fees, out of pocket expenses, liability, applicable law, etc.*]

1.9 Scope of Work – Compulsory Report Format and Procedures to be Performed

Independent Report of Factual Findings on costs claimed under a Grant Agreement financed under the Seventh Research Framework Programme (FP7)

To be printed on letterhead paper of the Auditor

<Name of contact person(s)>, < Position>
< Beneficiary's name>
<Address>
<dd Month yyyy>
In accordance with our contract dated <dd Month yyyy> with <name of the Beneficiary> "the Beneficiary" and the terms of reference attached thereto (appended to this Report), we provide our Independent Report of Factual Findings ("the Report"), as specified below.

Objective

We *[legal name of the audit firm]*, established in *[full address/city/state/province/country]* represented for signature of this Report by [*[name and function of an authorised representative]* have performed agreed-upon procedures regarding the cost declared in the Financial Statement(s)[2] of [*name of beneficiary*] hereinafter referred to as the Beneficiary, to which this Report is attached, and which is to be presented to the Commission of the European Communities under grant agreement *[EC grant agreement reference: title, acronym, number]* for the following period(s) *[insert period(s) covered by the Financial Statement(s) per Activity]*. This engagement involved performing certain specified procedures, the results of which the European Commission uses to draw conclusions as to the eligibility of the costs claimed.

Scope of Work

Our engagement was carried out in accordance with :

- the terms of reference appended to this Report and:

- International Standard on Related Services ('ISRS') 4400 *Engagements to perform Agreed-upon Procedures regarding Financial Information* as promulgated by the International Federation of Accountants ('IFAC);

- the *Code of Ethics for Professional Accountants* issued by the IFAC. Although ISRS 4400 provides that independence is not a requirement for agreed-upon procedures engagements, the European Commission requires that the Auditor also complies with the independence requirements of the *Code of Ethics for Professional Accountants;*

As requested, we have only performed the procedures set out in the terms of reference for this engagement and we have reported our factual findings on those procedures in the table appended to this Report.

The scope of these agreed upon procedures has been determined solely by the European Commission and the procedures were performed solely to assist the European Commission in evaluating whether the costs claimed by the Beneficiary in the accompanying Financial Statement has been claimed in accordance with the Grant Agreement. The Auditor is not responsible for the suitability and appropriateness of these procedures.

[2] Financial Statement in this context refers solely to Form C - Annex VI by which the Beneficiary claims costs under the Grant Agreement.

Because the procedures performed by us did not constitute either an audit or a review made in accordance with International Standards on Auditing or International Standards on Review Engagements, we do not express any assurance on the Financial Statements.

Had we performed additional procedures or had we performed an audit or review of the Financial Statements of the Beneficiary in accordance with International Standards on Auditing, other matters might have come to our attention that would have been reported to you.

Sources of Information

The Report sets out information provided to us by the management of the Beneficiary in response to specific questions or as obtained and extracted from the Beneficiary's information and accounting systems.

Factual Findings

The above mentioned Financial Statement(s) per Activity was (were) examined and all procedures specified in the appended table for our engagement were carried out. On the basis of the results of these procedures, we found:
All documentation and accounting information to enable us to carry out these procedures has been provided to us by the Beneficiary. Except as indicated below, no exceptions were noted.

Exceptions

- In some cases, the Auditor was not able to successfully complete the procedures specified. These exceptions are as follows**:**

exceptions such as inability to reconcile key information, unavailability of data which prevented the Auditor from carrying out the procedures, etc. should be listed here. The Commission will use this information to decide the amounts which will be reimbursed.

Use of this Report

This Report is solely for the purpose set forth in the above objective.

This Report is prepared solely for the confidential use of the Beneficiary and the European Commission and solely for the purpose of submission to the European Commission in connection with the requirements as set out in Article II.4.4 of the Grant Agreement. This Report may not be relied upon by the Beneficiary or by the European Commission for any other purpose, nor may it be distributed to any other parties. The European Commission may only disclose this Report to others who have regulatory rights of access to it, in particular the European Anti Fraud Office and the European Court of Auditors.

This Report relates only to the Financial Statement(s) specified above and does not extend to any other financial statements of the Beneficiary.

No conflict of interest exists between the Auditor and the Beneficiary in establishing this Report. The fee paid to the Auditor for providing the Report was € _____.

We look forward to discussing our Report with you and would be pleased to provide any further information or assistance which may be required.

[legal name of the audit firm]
[[name and function of an authorised representative]

Procedures performed by the Auditor

The Auditor designs and carries out his work in accordance with the objective and scope of this engagement and the procedures to be performed as specified below. When performing these procedures the Auditor may apply techniques such as inquiry and analysis, (re)computation, comparison, other clerical accuracy checks, observation, inspection of records and documents, inspection of assets and obtaining confirmations or any others deemed necessary in carrying out these procedures.

The European Commission reserves the right to issue guidance together with example definitions and findings to guide the Auditor in the nature and presentation of the facts to be ascertained. The European Commission reserves the right to vary the procedures by written notification to the Beneficiary. The procedures to be performed are listed as follows:

Procedures	**Standard factual finding and basis for exception reporting**
Personnel Costs	
1. Recalculate hourly personnel and overhead rates for personnel (full coverage if less than 20 employees, otherwise a sample of minimum 20, or 20% of employees, whichever is the greater), indicate the number of productive hours used and hourly rates. Where sampling is used, selection should be random with a view to producing a representative sample. **'Productive hours'** represent the (average) number of hours made available by the employee in a year after the deduction of holiday, sick leave and other entitlements. This calculation should be provided by the Beneficiary. [if average costs are used, a separate independent report is required on the methodology]	For each employee in the sample of ___, the Auditor obtained the personnel costs (salary and employer's costs) from the payroll system together with the productive hours from the time records of each employee. For each employee selected, the Auditor recomputed the hourly rate by dividing the actual personnel costs by the actual productive hours, which was then compared to the hourly rate charged by the Beneficiary. No exceptions were noted. The average number of productive hours for the employees selected was _____. **If the productive hours or costs of personnel cannot be identified, they should be listed (together with the amounts) as exceptions in the main report.**
2. For the same selection examine and describe time recording of employees (paper/ computer, daily/weekly/monthly, signed, authorised).	Employees record their time on a daily/ weekly/ monthly basis using a paper/computer-based system. The time-records selected were authorised by the project manager or other superior. **If no time records are available which fit the above description, this should be listed as an exception in the main report.**
3. Employment status and employment conditions of personnel. The Auditor should obtain the employment contracts of the employees selected and compare with the standard employment contract used by the Beneficiary. Differences which are not foreseen by the Grant Agreement should be noted as exceptions.	For the employees selected, the Auditor inspected their employment contracts and found that they were: – directly hired by the Beneficiary in accordance with its national legislation, – under the sole technical supervision and responsibility of the latter, and – remunerated in accordance with the normal practices of the Beneficiary. **Personnel who do not meet all three conditions should be listed (together with the amounts) as exceptions in the main report.**
4. Use of average personnel costs	The Auditor found that the personnel costs charged to the financial statement:

Procedures	Standard factual finding and basis for exception reporting
	- are calculated using average costs in accordance with the methodology as specified in the Report of findings on the methodology dated _____. - have been calculated using amounts derived from the relevant period which can be reconciled to the accounting records of the relevant period. The Auditor obtained confirmation from the Beneficiary that the rates used were not budgeted or estimated amounts. **If amounts cannot be reconciled, or if estimates or budgeted amounts were used, this should be reported as an exception in the main report.**
Subcontracting	
5. Obtain a written description from the Beneficiary regarding 3rd party resources used and compare with Annex 1 to the Grant Agreement.	The Auditor compared the description of the 3rd party resources provided by the Beneficiary to the specification in Annex 1 to the Grant Agreement, and found them to be the same **If the descriptions do not clearly match, this should be reported as an exception in the main report.**
6. Inspect documents and obtain confirmations that subcontracts are awarded according to a procedure including an analysis of best value for money (best price-quality ratio), transparency and equal treatment. Full coverage if less than 20 items, otherwise a sample of minimum 20, or 20% of the items, whichever is the greater.	The Auditor obtained tendering documents for each subcontract entered into and found that the tendering process was followed and that a written analysis of value-for-money had been prepared by the Beneficiary in support of the final choice of subcontractor, or that the contract had been awarded as part of an existing framework contract entered into prior to the beginning of the project. **If the Auditor is not provided with evidence of either of the above situations, the amount of the subcontract should be listed as an exception in the main report.**
Other Direct Costs	
7. Allocation of equipment subject to depreciation is correctly identified and allocated to the project. Full coverage if less than 20 items, otherwise a sample of minimum 20, or 20% of the items, whichever is the greater.	The Auditor traced the equipment charged to the project to the accounting records and the underlying invoices. The Beneficiary has documented the link with the project on the invoice and purchase documentation, and, where relevant, the project accounting. The asset value was agreed to the invoice and no VAT or other identifiable indirect taxes were charged. The depreciation method used to charge the equipment to the project was compared to the Beneficiary's normal accounting policy and found to be the same. **If assets have been charged which do not comply with the above, they should be listed (together with the amounts) as exceptions in the main report.**
8. Travel costs correctly identified and allocated to the project (and in line with Beneficiary's normal policy for non-EC work regarding first-class travel, etc.) Full coverage if less than 20 items, otherwise a sample of minimum 20, or 20% of the items, whichever is the greater. The Beneficiary should provide written evidence of its normal policy for travel costs (e.g. use of first class tickets) to enable the Auditor to compare the travel charged with this policy.	The Auditor inspected the sample and found that the Beneficiary had allocated travel costs to the project by marking of invoices and purchase orders with the project reference, resulting in traceable allocation in the project accounts. The costs charged were compared to the invoices and found to be the same. No VAT or other identifiable indirect taxes were charged. The use of first class travel was in line with the written policy provided by the Beneficiary. **Costs which are not allocated to project accounts and do not have a clear attribution (normally by writing the project number on the original invoice) should be listed (together with the amounts) as exceptions in the main report.**
9. Consumables correctly identified and allocated to the project. Full coverage if less than 20 items, otherwise a sample of	The Auditor inspected the sample and found that the Beneficiary had allocated consumable costs to the project by marking of invoices and purchase orders with the project reference, resulting in traceable

Procedures	Standard factual finding and basis for exception reporting
minimum 20, or 20% of the items, whichever is the greater.	allocation in the project accounts. The costs charged were compared to the invoices and found to be the same. No VAT or other identifiable indirect taxes were charged. **Costs which are not allocated to project accounts and do not have a clear attribution (normally by writing the project number on the original invoice) should be listed (together with the amounts) as exceptions in the main report.**
Indirect costs	
10. Obtain and review a detailed breakdown of Indirect costs (reconciled to the financial accounts) and confirm that the following costs are not present: a) identifiable indirect taxes including value added tax, b) duties, c) interest owed, d) provisions for possible future losses or charges, e) exchange losses, cost related to return on capital, f) costs declared or incurred, or reimbursed in respect of another Community project, g) debt and debt service charges, excessive or reckless expenditure[3].	The Auditor obtained the total overhead amount which was allocated and reconciled this to the accounting records for the period in question. The Auditor recalculated the ratio of indirect costs [*choose one:* as a percentage of personnel costs/ as an hourly rate] and agreed it to the rate used in the Financial Statement(s). The Auditor obtained a detailed breakdown from the accounting system of the indirect costs which have been charged to the contract, and reconciled the individual amounts to the general ledger of the Beneficiary. The Auditor found that costs for the non-research activities of the Beneficiary, such as manufacturing, education, marketing of products or services, etc., had not been included in the calculation. For each element of the breakdown, the Auditor obtained the Beneficiary's confirmation that it contained none of the ineligible costs specified (typical examples are leasing costs, loan charges, provisions for doubtful debt (but not normal accruals), local business and property taxes, customs duties, exchange losses from billing in a foreign currency). **Only the types of excessive and reckless expenditure listed in the Commission's guidance should be considered, the Auditor is not required to exercise professional judgement or provide assurance in this matter.** **Amounts which do not meet the above criteria or where the Auditor is not provided with sufficient information in order to inspect and compare the types of cost should be listed (together with the amounts) as exceptions in the main report.**
11. Assess use of a simplified method of calculation of overheads at the level of the legal entity. The Beneficiary may use a simplified method of calculation (either due to the lack of analytical accounting or legal requirement to use a form of cash-based accounting). This does not permit the use of a generalised estimate, or the use of a 'standard' rate that is not derived from the financial accounts of the period in question. Thus the rate (but not the methodology) should be updated for each accounting period.	The Beneficiary's accounting system does not permit indirect costs to be separately identified for the individual departments. **[and/ or]** The Beneficiary's accounting system is cash-based and year-end adjustments are made using accounting estimates in order to charge certain accrued costs. The Auditor obtained the breakdown of overhead costs and the adjusting entries together with the source of the relevant accounting entries. The Beneficiary provided the Auditor with underlying calculations showing the basis for additional

[3] Excessive or reckless expenditure as defined in guidance note to be issued by the Commission in 2007.

Procedures	Standard factual finding and basis for exception reporting
	accounting entries. The Auditor agreed these calculations to the relevant sources of management information. **Any elements of a simplified calculation which represent percentage estimates and which cannot be compared to underlying data should be listed (together with the amounts) as exceptions in the main report.**
12. Inspect and compare exchange rates into Euros.	The Auditor compared the exchange rates used for conversion with the applicable official exchange rates established by the European Communities and the Beneficiary used [choose one]: • the conversion rate of the date where the actual costs were incurred • the rate applicable on the first day of the month following the end of reporting period **Where rates cannot be agreed, an exception should be noted, (together with the amount) in the main report.**
13. Identification of receipts. The Beneficiary is obliged to deduct from its claim any receipts related to the project (income from events, rebates from suppliers, etc.)	The Auditor examined the relevant project accounts and obtained representations from the Beneficiary that the amounts listed represent a complete record of the sources of income connected with the project. The amount included in the claim regarding receipts is the same as the amount recorded in the project accounting. **Any discrepancies in the receipts noted in the accounts and those reported by the Beneficiary should be noted (together with the amount) as exceptions in the main report.**
14. Identification of interest yielded on pre-financing. The Beneficiary, when it is the coordinator of the project, is obliged to declare interest yielded on pre-financing	The Auditor compared the relevant project accounts with the interest shown in the bank statements and found them to be the same. **Any discrepancies in the interest noted in the accounts and those reported by the Beneficiary should be noted (together with the amount) as exceptions in the main report.**