ISTITUTO PER LO STUDIO
E LA PREVENZIONE ONCOLOGICA

DELIBERAZIONE DEL DIRETTORE GENERALE
(Nominato con D.P.G.R.T. n. 233 del 13/12/2010)

N° 178 del 30/12/2011

Oggetto: Progetto "Monitoring HPV Type prevelence in the post-vaccination era in women living in Basilicata region, Italy" finanziato dalla Ditta SANOFI Pasteur di Lione. Approvazione dello schema di accordo e recepimento del finanziamento.	
Struttura Proponente	S.C. Citologia Analitica e Biomolecolare
	Contabilità e Controllo di Gestione
Proposta n. 178	Responsabile del procedimento
	Estensore

IMMEDIATAMENTE ESEGUIBILE [X]

Importo di spesa:

Conto Economico n. 3A010302 "CONTRIBUTI DA ENTI E SOGGETTI PRIVATI"

Eseguibile a norma di Legge dal 30 DIC. 2011

Pubblicato a norma di Legge il 30 DIC. 2011

Inviato al Collegio Sindacale il 30 DIC. 2011

L'anno 2011, il giorno 30 del mese di DICEMBRE
Il sottoscritto Prof. Gianni Amunni, nella sua qualità di

DIRETTORE GENERALE

di questo Istituto per lo Studio e la Prevenzione Oncologica , con sede in Via Cosimo Il Vecchio 2 – 50139 Firenze, in forza del Decreto del Presidente della Giunta Regionale Toscana n. 233 del 13/12/2010.

Visto il D. Lgs.vo 30/12/1992 n. 502 e sue successive modifiche ed integrazioni e la L. R. Toscana n. 40 del 24/02/2005 di disciplina del Servizio Sanitario Regionale e successive modificazioni ed integrazioni;

vista la legge regionale 4 febbraio 2008, n. 3, ai sensi della quale è stato istituito l'ISPO – Istituto per lo Studio e la Prevenzione Oncologica - "ente del servizio sanitario regionale, dotato di personalità giuridica pubblica e di autonomia organizzativa, amministrativa e contabile" (art.1), il quale ai sensi dell'art.19, comma 1 della citata legge subentra nelle attività già esercitate dal CSPO " a far data dal 1 luglio 2008";

vista la delibera del Direttore Generale n. 5 del 14.07.2008 con la quale è stato approvato il regolamento dell'ISPO;

vista la delibera del Direttore Generale n. 85 del 18.05.09 con la quale è stato approvato il regolamento dei progetti finalizzati;

premesso che:

- la Ditta SANOFI Pasteur MSD S.N.C., Rue Jonas Salk n. 8, 69007 Lione, Francia è una azienda francese leader nel settore farmaceutico specializzata nello sviluppo, nella registrazione e nella distribuzione di vaccini per uso umano nei paesi che costituiscono l'Unione Europea (UE);
- nell'ambito delle sue attività di ricerca è promotore di uno studio epidemiologico denominato "Monitoring HPV Type prevelence in the post-vaccination era in women living in Basilicata region, Italy" - SIN Code GDS02E;
- per la corretta implementazione e svolgimento dello studio, la Ditta SANOFI Pasteur ha selezionato l'Istituto per lo Studio e la Prevenzione Oncologica che ha personale qualificato e la struttura necessaria per eseguire i servizi relativi allo studio;
- come Coordinatore Scientifico dello Studio nonché Responsabile del Progetto per ISPO è stata individuata la Dr.ssa Francesca Carozzi , Biologo Dirigente presso la S.C. Citologia Analitica e Biomolecolare I.S.P.O.per la sua esperienza di laboratorio;
- con Delibera del Direttore Generale ISPO n. 215 del 27.12.2010 è stato approvato lo Studio di Fattibilità per la valutazione dello studio epidemiologico "Monitoring HPV Type prevelence in the post-vaccination era in women living in Basilicata region, Italy":
- il suddetto Studio di Fattibilità si è concluso il 30.04.2011 e alla scadenza si è convenuto di affidare l'esecuzione dello Studio "Monitoring HPV Type prevelence in the post-vaccination era in women living in Basilicata region, Italy" all'ISPO;

visto lo schema dell'accordo tra ISPO e SANOFI Pasteur MSD S.N.C., avente ad oggetto lo Studio "Monitoring HPV Type prevelence in the post-vaccination era in women living in Basilicata region, Italy", documento in versione affiancata italiano e inglese allegato alla presente deliberazione a farne parte integrante e sostanziale (Allegato "A");

considerato che il contenuto dello schema dell'accordo per lo Studio "Monitoring HPV Type prevelence in the post-vaccination era in women living in Basilicata region, Italy", è stato condiviso da entrambe le parti;

preso atto che l'accordo sopracitato decorre dalla data dell'ultima sottoscrizione e termina il 31.12.2014 e che la Ditta SANOFI Pasteur MSD S.N.C corrisponderà ad ISPO per i servizi resi, così come elencati in dettaglio nell'allegato "1" dello schema di accordo, la somma totale di € 880.770,00 IVA esclusa secondo le modalità di cui all'allegato "2" dello schema di accordo;

ritenuto pertanto opportuno di approvare lo schema di accordo recependo il finanziamento pari a € 880.770,00 IVA esclusa;

ritenuto di dichiarare il presente atto immediatamente eseguibile per permettere poter partire quanto prima con lo studio epidemiologico "Monitoring HPV type prevalence in the post-vaccination era in women living in Basilicata Region, Italy";

Con il parere favorevole del Direttore Sanitario

DELIBERA

Per quanto esposto in narrativa, formante parte integrante e sostanziale del presente atto:

1. di approvare lo schema di accordo per la realizzazione dello Studio epidemiologico "Monitoring HPV type prevalence in the post-vaccination era in women living in Basilicata Region, Italy" da parte di ISPO per la Ditta SANOFI, allegato "A" alla presente quale parte integrante e sostanziale;

2. di prendere atto che la Ditta SANOFI Pasteur MSD S.N.C. corrisponderà ad I.S.P.O. per i servizi resi, così come elencati nel dettaglio nell'allegato "1" dello schema di accordo per lo Studio di Fattibilità, la somma totale di € 880.770,00 IVA esclusa, secondo le modalità di cui all'allegato 2 dello schema di accordo;

3. di dare atto che la disponibilità finanziaria totale è di € 880.770,00 Iva esclusa, imputata a valere sull'autorizzazione n° 96/11, cdc 671 Conto Economico 3A010302 "CONTRIBUTI DA ENTI E SOGGETTI PRIVATI";

4. di dichiarare il presente atto immediatamente eseguibile ai sensi della normativa vigente;

5. di trasmettere il presente atto all'albo di pubblicità degli atti di questo Istituto al Collegio Sindacale.

IL DIRETTORE GENERALE
Gianni Amunni

IL DIRETTORE SANITARIO
Chiara Neri

Eleenco degli allegati

Allegato A	Schema di accordo tra ISPO e Ditta Sanofi Pasteur	pagg. 104

Strutture aziendali da partecipare:

S.C. Citologia Analitica e Biomolecolare, ISPO;
S.S. Contabilità e Controllo di Gestione ISPO;
Gestione Amministrativa Progetti ISPO;
Supporto Amministrativo Attività Scientifica e di Ricerca ISPO;
Dipartimento Amministrazione e Finanza ASF.

ALLEGATO DI DELIBERA "A" ALLA DELIBERA D.G. N. 178 del 30/12/2011

EPIDEMIOLOGICAL STUDY SERVICES AGREEMENT	ACCORDO PER I SERVIZI RIGUARDANTI LO STUDIO EPIDEMIOLOGICO

THIS AGREEMENT IS MADE BY AND BETWEEN:

- **SANOFI PASTEUR MSD S.N.C.**
  A "Société en Nom Collectif" duly existing and organized under the laws of France, with a capital of 60.000.000 Euros, having its registered office located at 8, rue Jonas Salk, 69007 LYON, France and registered in LYON under SIREN n° 392 032 934 RCS Lyon

  Represented by Dr Jean-Paul KRESS, President

  Hereinafter referred to as "**SPMSD**"

AND

- **THE ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA (ISPO)**
  An organisation duly existing and organized under the laws of Italy and having its registered office at Via Cosimo il Vecchio 2, 50139 FIRENZE, Italy

  Represented by Dr. Dott. Gianni AMUNNI, General Manager

  Hereinafter referred to as "**the INSTITUTION**"

IN THE PRESENCE OF:

- **The Doctor Francesca CAROZZI**
  A biologist who conducts her professional activities at the ISPO

  Hereinafter referred to as the "**Scientific Coordinator**"

SPMSD and the INSTITUTION hereinafter also being collectively referred to as the "**Parties**" and individually referred to as the "**Party**".

WHEREAS

SPMSD is a French leading pharmaceutical company specialized in the development, registration and distribution of vaccines for human use in the countries which composed the European Union (EU) as of May 1st, 2004 (i.e. excluding the ten acceding countries that joined the EU on May 1st, 2004) and the four countries of the European Free Trade Association.

IL PRESENTE ACCORDO E' STIPULATO DA E TRA:

- **SANOFI PASTEUR MSD S.N.C.**
  Una "Società in nome collettivo" debitamente costituita ed esistente ai sensi delle leggi francesi, con capitale sociale di Euro 60.000.000, avente sede legale in rue Jonas Salk 8, 69007, Lione, Francia, e registrata a Lione al SIREN n. 392 032 934 RCS Lione

  Rappresentata dal Dott. Jean-Paul KRESS, Presidente

  Di seguito definita "**SPMSD**"

E

- **L'ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA (ISPO)**
  Una organizzazione debitamente costituita ed esistente ai sensi delle leggi italiane ed avente sede legale in Via Cosimo il Vecchio 2, 50139 FIRENZE, Italy

  Rappresentata dal Dott. Gianni AMUNNI, Direttore Generale

  Di seguito definita "**l'ISTITUZIONE**"

ALLA PRESENZA DI:

- **La Dott.ssa Francesca CAROZZI**
  Una biologa che presta la propria attività professionale presso l'ISPO

  Di seguito definita "**Coordinatore Scientifico**"

SPMSD e l'ISTITUZIONE di seguito anche definite congiuntamente le "**Parti**" ed individualmente la "**Parte**".

PREMESSO CHE

SPMSD è una azienda francese leader nel settore farmaceutico specializzata nello sviluppo, nella registrazione e nella distribuzione di vaccini per uso umano nei paesi che costituiscono l'Unione Europea (UE) alla data del 1 maggio 2004 (ovverosia con l'esclusione dei dieci paesi che sono entrati nell'UE il 1 maggio 2004) e nei quattro paesi dell'Associazione Europea per il Libero Scambio (EFTA).

Within the framework of its research activities, SPMSD is sponsor of an epidemiological study entitled "*Monitoring HPV type prevalence in the post-vaccination era in women living in the Basilicata region, Italy*" – *SIN Code GDS02E* (hereinafter referred to as the "**Study**").

Nell'ambito delle sue attività di ricerca, SPMSD è il promotore di uno studio epidemiologico denominato "*Monitoring HPV type prevalence in the post-vaccination era in women living in the Basilicata region, Italy*" – *SIN Code GDS02E* (di seguito lo "**Studio**").

For the good implementation of the Study, SPMSD has selected the INSTITUTION that has capable personnel and the necessary accommodation to perform the Study related Services (as defined below).

Per la corretta implementazione dello Studio, SPMSD ha selezionato l'ISTITUZIONE cha ha personale qualificato e la struttura necessaria per eseguire i servizi relativi allo Studio (come di seguito delineati).

With the INSTITUTION's consent, SPMSD has selected the Scientific Coordinator because of her expertise in laboratory to carry out work for the Study.

Con il consenso dell'ISTITUZIONE, SPMSD ha selezionato il Coordinatore Scientifico per la sua esperienza di laboratorio al fine di portare avanti il lavoro per lo Studio.

The INSTITUTION and the Scientific Coordinator have accepted to perform some services for SPMSD within the framework of the Study. A former agreement dated 30 December 2010 was executed between the Parties in order to assess the feasibility of the Study (hereinafter referred to as the "**Feasibility Agreement**").

L'ISTITUZIONE ed il Coordinatore Scientifico hanno accettato di eseguire alcune prestazioni professionali per SPMSD nell'ambito dello Studio. Un precedente accordo datato 30 Dicembre 2010 è stato sottoscritto tra le Parti, al fine di valutare la fattibilità dello Studio (di seguito denominato "**Accordo di Fattibilità**").

After the performance by the INSTITUTION and the Scientific Coordinator of some specific services under the Feasibility Agreement, the Parties are willing now to confide to the INSTITUTION the performance of some other services relating to the main phase of the Study.

Dopo l'esecuzione da parte dell'ISTITUZIONE e del Coordinatore Scientifico di alcune specifiche prestazioni professionali ai sensi dell'Accordo di Fattibilità, le Parti sono ora decise ad affidare all'ISTITUZIONE l'esecuzione di ulteriori prestazioni professionali concernenti la fase principale dello Studio.

The INSTITUTION and the Scientific Coordinator accept to perform such services in the terms and conditions set forth hereunder.

L'ISTITUZIONE ed il Coordinatore Scientifico accettano di eseguire tali prestazioni nei termini ed alle condizioni di seguito stabiliti.

NOW THEREFORE

PERTANTO

In consideration of the foregoing promises and the mutual promises and the conditions herein contained, SPMSD and the INSTITUTION agree as follows on the following terms and conditions.

In considerazione delle suesposte premesse, dei reciproci impegni e delle condizioni qui contenute, SPMSD e l'ISTITUZIONE si accordano come segue ai seguenti termini e condizioni.

ARTICLE 1 – DEFINITIONS

ARTICOLO 1 – DEFINIZIONI

1.1 Unless stated otherwise, the following terms shall have the meanings hereby assigned when used in this Agreement:

1.1 Salvo quanto diversamente indicato, i seguenti termini avranno il significato qui attribuito quando utilizzati nel presente Accordo:

"**Advisory Board**" means the scientific board whose role is to validate the Protocol and the Study Reports in their interim and final version, and to validate any publications related to the Study. The Advisory Board is composed of independent Experts (as defined below).

"**Consiglio di Sorveglianza**" indica il comitato scientifico il cui ruolo è quello di validare il Protocollo e le Relazioni dello Studio nelle rispettive bozze e nella versione finale, nonchè di validare ogni pubblicazione connessa con lo Studio. Il Consiglio di Sorveglianza è composto da Esperti indipendenti (come definito di seguito).

"**Agreement**" means the present epidemiological Study Services Agreement and any and all amendments or annexes attached thereto that shall be made a part of this Agreement for all purposes and any and all other applicable terms, conditions and policies referenced in any of the preceding documents.

"**Accordo**" indica il presente Accordo per i Servizi riguardanti lo Studio Epidemiologico, inclusi tutti gli emendamenti o gli allegati che ne formeranno parte integrante per qualsivoglia finalità nonchè tutti gli ulteriori termini, condizioni e linee di condotta menzionate nei precedenti documenti.

"**Central Laboratory**" means the Laboratory of the INSTITUTION in charge of laboratory testing such as Hybrid Capture 2 (HC2) tests, HPV genotyping and the quality control for some cytological samples.

"**Laboratorio Centrale**" indica il Laboratorio dell'ISTITUZIONE incaricato di effettuare i test di laboratorio quali il Hybrid Capture 2 (HC2), la genotipizzazione HPV ed il controllo di qualità per alcuni campioni citologici .

"**Center**" means the health care practices where all Study-related activities are conducted (Local Health Unit (LHU) of Matera).

"**Centro**" indica gli ambulatori sanitari dove vengono condotte tutte le attività connesse allo Studio (Azienda Sanitaria Locale (ASL) di Matera).

"**Coordinating Investigators**" means the Screening Investigator, Doctor Pasquale Silvio Anastasio and the Vaccination Investigator, Doctor Espedito Antonio Moliterni who are the selected physicians responsible for the conduct of the Study in the LHU of Matera.

"**Sperimentatori Coordinatori**" indica lo Sperimentatore di Screening, Dott. Pasquale Silvio Anastasio, e lo Sperimentatore della Vaccinazione, Dott. Espedito Antonio Moliterni, i quali rappresentano i medici responsabili della conduzione dello Studio nella ASL di Matera.

"**CRO**" means the contract research organization specialized in the conduct of epidemiological studies and in charge of the Study monitoring activities performed by its epidemiological research associates (ERAs), i.e. Omnicare Clinical Research SARL, commercially operating as Theorem Clinical Research SARL, a company duly existing and organised under the laws of France and having its registered office at 40/50 rue Auguste Blanqui, 94250 Gentilly, France. The CRO will work in close co-operation during the Study with the INSTITUTION.

"**CRO**" indica l'organizzazione di ricerca a contratto specializzata nella conduzione di studi epidemiologici ed incaricata di eseguire le attività di monitoraggio dello Studio effettuate dai propri associati alla ricerca epidemiologica, (di seguito "ERAs"), ossia Omnicare Clinical Research SARL, commercialmente operante come Theorem Clinical Research SAR una società debitamente costituita ed esistente ai sensi delle leggi francesi, avente sede legale in 40/50 rue Auguste Blanqui, 94250 Gentilly, Francia. Durante lo Studio la CRO lavorerà in stretta collaborazione con l'ISTITUZIONE.

"**Daily Report**" means the document that the Coordinating Investigators will fill in for documenting the total number of Participants that could potentially participate in the Study and assessing the representativeness of the final Study sample.

"**Relazione Giornaliera**" indica il documento che gli Sperimentatori Coordinatori dovranno compilare per documentare il numero totale dei Partecipanti che potrebbero potenzialmente partecipare allo Studio e per valutare la rappresentatività del campione finale dello Studio.

"**Epidemiological Projects Coordinator** or "**EPC**" means SPMSD employee, in charge of the Study progress and coordination and who is Samantha ATRUX-TALLAU.

"**Coordinatore dei Progetti Epidemiologici**" o "**EPC**" indica il dipendente di SPMSD incaricato dello stato di avanzamento e della coordinazione dello Studio, che è Samantha ATRUX-TALLAU.

"**Epidemiology Project Manager**" or "**EPM**" means the SPMSD employee, in charge of supervising all epidemiological studies and EPC activities and who is Dr Laurence SERRADELL.

"**Manager dei Progetti Epidemiologici**" o "**EPM**" indica il dipendente di SPMSD, incaricato di supervisionare tutti gli studi epidemiologici e le attività degli EPC e che è il Dr Laurence SERRADELL.

"**Epidemiological Study Report**" or "**ESR**" means the report that is written by the INSTITUTION under the Services governed

"**Relazione dello Studio Epidemiologico**" o "**ESR**" indica la relazione redatta dall'ISTITUZIONE nell'ambito dei Servizi oggetto

by the present Agreement and that shall be delivered to SPMSD in its final and approved version.

"**Experts**" means the persons with recognized knowledge and expertise who are members of the Advisory Board/Steering Committee who are asked to give their opinion/expertise on the Study.

"**Informed Consent Form or ICF**" refers to the document that collects the informed consent of the Participants. Such document reflects the decision to take part in the Study, which must be written, dated and signed, taken freely after being duly informed of the nature, significance, implications and risks of the Study, and appropriately documented, by any of the Participants, or where the Participants are not capable of giving consent, by any legal representative.

"**Key Personnel**" means the contacts at the INSTITUTION who shall have the main function in the Study and who works with the Scientific Coordinator.

"**Parent Companies**" means any company holding directly or indirectly fifty percent (50%) or more of SPMSD capital stock or fifty percent (50%) or more of its voting rights.

"**Participant**" means any individual who participates in the Study.

"**Participant Form**" means the printed, optical or electronic document designed to record all of the Protocol required information to be reported to SPMSD, on each Study Participant and completed by the Coordinating Investigators or delegates.

"**Protocol**" means the document that describes the objectives, design, methodology, statistical considerations and organization of the Study. The term protocol refers to the protocol, its successive versions and its amendments.

The Protocol in its version dated 24 June 2011 is attached in Annex 1 as a part hereof. It is agreed that the present Agreement shall be governed by the most recent version of the Protocol. Should the present Agreement to be executed prior to availability of the final version of the Protocol, the last-dated version of the Protocol thereof will be considered to be incorporated by reference in place of any prior versions. In case there is a conflict between the terms of the Protocol and those of the

del presente Accordo e che sarà consegnata a SPMSD nella sua versione finale e approvata.

"**Esperti**" indica le persone con riconosciuta conoscenza ed expertise che sono membri del Consiglio di Sorveglianza/Comitato operativo ed alle quali è richiesto di fornire la loro opinione/expertise nello Studio.

"**Modulo per il consenso informato o ICF**" indica il documento che raccoglie il consenso informato delle Partecipanti. Tale documento rispecchia la decisione di prendere parte allo Studio, che deve essere espressa per iscritto, datata e firmata, presa liberamente dopo essere stati debitamente informati sulla natura, sul significato, sulle implicazioni e sui rischi dello Studio, ed adeguatamente documentata, da ciascuno delle Partecipanti, o qualora le Partecipanti non fossero in grado di prestare il consenso, da ciascun legale rappresentante.

"**Personale Qualificato**" indica i contatti presso l'ISTITUZIONE che avranno i compiti principali nello Studio e che lavoreranno con il Coordinatore Scientifico.

"**Società Controllanti**" indica ogni società che detiene direttamente o indirettamente il cinquanta per cento (50%) o più delle azioni di SPMSD o il cinquanta per cento (50%) o più dei suoi diritti di voto.

"**Partecipante**" indica ogni individuo che partecipa allo Studio.

"**Modulo dei Partecipanti**" indica il documento stampato, ottico o elettronico adibito a registrare tutte le informazioni richieste dal Protocollo da comunicare a SPMSD, su ogni Partecipante allo Studio e compilato dagli Sperimentatori Coordinatori o da loro rappresentanti.

"**Protocollo**" indica il documento che descrive gli obiettivi, il disegno, la metodologia, le considerazioni statistiche e l'organizzazione dello Studio. Il termine protocollo si riferisce al protocollo, alle sue successive versioni ed emendamenti.

Il Protocollo nella sua versione datata 24 giugno 2011 è accluso nell'Allegato 1 come parte integrante di questo Accordo. Si conviene che il presente Accordo sarà regolato dalla versione più recente del Protocollo. Nel caso in cui il presente Accordo dovesse essere esecutivo prima che sia disponibile la versione finale del Protocollo, la versione più recente dello stesso sarà considerata incorporata mediante rinvio in luogo di ogni precedente versione. In caso di conflitto tra i termini del Protocollo e quelli dell'Accordo, i termini del

Agreement, the terms of the present Agreement will govern with respect to contract provisions and conditions but the terms of the attached Protocol will govern with respect to the conduct of the Study and with respect to serving the best interests of the Participants' welfare.

presente Accordo prevarranno relativamente alle clausole e condizioni del contratto ma i termini dell'allegato Protocollo prevarranno per quanto attiene alla conduzione dello Studio e per la miglior tutela del benessere dei Partecipanti.

"Sample" means any cervical material collected by the Coordinating Investigators in compliance with the Protocol conditions of inclusion into the Study.

"Campione" indica ogni materiale cervicale raccolto dagli Sperimentatori Coordinatori nel rispetto delle condizioni del Protocollo per l'inclusione nello Studio.

"Scientific Coordinator" means the selected expert responsible for the Study-related Services, as more detailed in 4.3.

"Coordinatore Scientifico" indica l'esperto selezionato, responsabile dei Servizi dello Studio, come meglio dettagliato nell'art. 4.3.

"Services" means the services to be provided by the INSTITUTION pursuant to this Agreement as described in article 4.2 hereunder and in the list of activities as defined in the Annex 2 of this Agreement.

"Servizi" indica i servizi che l'ISTITUZIONE deve fornire conformemente al presente Accordo, come descritti nell'art. 4.2 che segue e nell'elenco delle attività come definite nell'allegato 2 del presente Accordo.

"SPMSD Local Contact" means the following wholly-owned subsidiary company: Sanofi Pasteur MSD located at Via degli Aldobrandeschi, 15 - 00163 ROMA - ITALY, who will be the local contact of the INSTITUTION during the Study on behalf of SPMSD. The Local Contact is Emilia PERINETTI, . Clinical & Epidemiology Manager.

"Contatto Locale di SPMSD" indica la seguente società interamente controllata: Sanofi Pasteur MSD, avente sede legale in Via degli Aldobrandeschi, 15 - 00163 ROMA - ITALIA, che sarà il contatto locale dell'ISTITUZIONE durante lo Studio per conto di SPMSD. Il Contatto Locale sarà Emilia PERINETTI, Manager Clinico ed Epidemiologico.

"Sponsor" means the company responsible for the initiation, management and financing of the Study and who is SPMSD.

"Promotore" indica la società responsabile dell'avvio, della gestione e del finanziamento dello Studio, che è SPMSD.

"Steering Committee" or "SC" means the group composed of the Scientific Coordinator, Coordinating Investigators, Sponsor representatives (epidemiologist, EPM, EPC...), INSTITUTION representatives (epidemiologist, biostatistician,...) and others who oversee the Study development, implementation, conduct, analysis and dissemination of Study Results.

"Comitato Operativo" or "SC" indica il gruppo composto dal Coordinatore Scientifico, dagli Sperimentatori Coordinatori, dai rappresentanti dello Sponsor (epidemiologo, EPM, EPC, ...), dai rappresentanti dell'ISTITUZIONE (epidemiologo, esperto di biostatistica ...) ed altri che sovraintendono lo sviluppo dello Studio, l'implementazione, la conduzione, l'analisi e la divulgazione dei Risultati dello Studio.

"Study Database" means the computerized structured collection of the Study data that will be set up within the Study by the INSTITUTION and/or the Scientific Coordinator and that will be delivered to SPMSD.

"Database dello Studio" indica la raccolta computerizzata dei dati dello Studio che sarà creato durante lo Studio dall'ISTITUZIONE e/o dal Coordinatore Scientifico e che sarà consegnato a SPMSD.

"Study Results" means any and all the results arising out from the Study such as but not limited to Study population data and HPV tests results.

"Risultati dello Studio" indica tutti e ciascun risultato derivante dallo Studio come, ma non solo, i dati sulla popolazione dello Studio e i risultati dei test HPV.

"Study Reports" means any and all Study-related reports arising out from the

"Relazioni dello Studio" indica ogni relazione relativa allo Studio che deriva dall'esecuzione dei

performance of the Services (such as but not limited to the data management plan, monitoring guidelines, monitoring reports, monthly status reports, statistical analysis reports, data management reports, interim reports and the ESR, etc.).

"Subsidiary Companies" means any company in which SPMSD holds directly or indirectly fifty percent (50%) or more of the capital stock or fifty percent (50%) or more of the voting rights.

"Territory" refers to the countries which composed the European Union (EU) as of May 1st, 2004 (i.e. excluding the ten acceding countries that joined the EU on May 1st, 2004) and the four countries of the European Free Trade Association.

1.2 Any reference to a statutory provision, code or guidance shall be deemed to include reference to any subsequent modification or re-enactment of it.

1.3 The headings to clauses, sections and paragraphs are inserted for convenience only and shall not affect the interpretation or construction of this Agreement.

1.4 Where appropriate, words denoting the singular shall include the plural and vice versa.

Servizi (come, ma non solo, il piano di gestione dati, le linee guida per il monitoraggio, i report di monitoraggio, i report mensili sullo stato dello Studio, i report sulle analisi statistiche, i report sulla gestione dei dati, i report provvisori e la ESR, ecc.).

"Società Controllate" indica ciascuna società in cui SPMSD detiene direttamente o indirettamente il cinquanta per cento (50%) o più delle azioni o il cinquanta per cento (50%) o più dei diritti di voto.

"Territorio" si riferisce ai paesi che fanno parte dell'Unione Europea (EU) alla data del 1 maggio 2004 (ovverosia con l'esclusione dei dieci paesi che sono entrati nell'UE il 1 maggio 2004) ed ai quattro paesi dell'Associazione Europea per il Libero Scambio (EFTA).

1.2 Qualsiasi riferimento a disposizioni normative, codici o linee guida dovrà intendersi come comprendente il riferimento ad ogni successiva modifica o nuova emanazione.

1.3 I titoli degli articoli, sezioni e paragrafi sono riportati solo per comodità e non influenzeranno l'interpretazione o il senso del presente Accordo.

1.4 Dove appropriato, le parole espresse al singolare ricomprenderanno il plurale e viceversa.

ARTICLE 2 – OBJECT

According to the terms of the present Agreement, SPMSD appoints the INSTITUTION who accepts such appointment, for the performance of some specific Study-related Services in accordance with Annex 2.

ARTICLE 2 –OGGETTO

In virtù del presente Accordo, SPMSD incarica l'ISTITUZIONE, che accetta tale incarico, di effettuare alcuni specifici Servizi connessi allo Studio secondo quanto stabilito nell'Allegato 2.

ARTICLE 3 – STUDY ORGANISATION

The Parties agree that the duties and obligations assigned to the INSTITUTION by virtue of the present Agreement will be performed according to the following planned calendar (hereinafter the **"Calendar"**), provided that no event required by SPMSD or at Centre (LHU of Matera) would postpone or delay the proper performance of the Study :

Action	Timelines
Regulatory documents preparation submission/approval	June 2010 - Nov 2011
Participant recruitment	Nov 2011 - April 2013

ARTICLE 3 – ORGANIZZAZIONE DELLO STUDIO

Le Parti convengono che i doveri e le obbligazioni attribuite all'ISTITUZIONE in virtù del presente Accordo saranno eseguiti secondo il seguente calendario programmato (di seguito il **"Calendario"**), purchè nessun evento richiesto da SPMSD o al Centro (ASL di Matera) possa posticipare o ritardare l'esecuzione dello Studio :

Azione	Tempistica
Predisposizione documenti regolatori presentazione/approvazione	Giugno 2010 –Nov. 2011
Reclutamento dei partecipanti	Nov. 2011- Aprile 2013

Laboratory analyses	Nov 2011 – May 2013
Database management (including hpv, pap test, vaccination status data entry)	Sept 2011 - June 2013
Quality control on database (ISPO with LHU)	Nov 2011 – July 2013
Statistical analyses	July 2013 – Sept 2013
Final study report	December 2013

If the actual start of the present Agreement is delayed or postponed for unavoidable justified reasons, the Calendar will extend beyond the dates described above for the number of days that the start of the Study was delayed or postponed, and all the Parties will be obliged to complete their respective warranties and obligations conferred by the present Agreement by that extended dates or as otherwise agreed in writing by the Parties.

ARTICLE 4 – OBLIGATIONS OF THE INSTITUTION

4.1 Compliance with epidemiological studies rules and regulations

4.1.1 During the performance of the Services, the INSTITUTION undertakes to abide by and to ensure that the Scientific Coordinator abides by the following laws, regulations and texts (hereinafter referred to as the "Texts"):

- the Protocol;
- the consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC
- the Declaration of Helsinki adopted in 1964, including its successive amendments
- the Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Ethical Review of Epidemiological Studies
- the EU Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data and any local enacting legislation such as the Italian Legislative decree n° 196 of June 30,

Analisi di laboratorio	Nov. 2011- Maggio 2013
Gestione del database (inclusi hpv, pap test, immissione dati sullo stato della vaccinazione)	Sett. 2011- Giugno 2013
Controllo di qualità sul database (ISPO e ASL)	Nov. 2011-Luglio 2013
Analisi statistica	Luglio 2013–Sett. 2013
Relazione finale dello Studio	Dicembre 2013

Nel caso in cui l'inizio del presente Accordo fosse ritardato o posticipato per una causa giustificata ed inevitabile, il Calendario sarà esteso oltre le date sopra indicate per un numero di giorni pari a quelli del ritardo o della posticipazione dell'inizio dello Studio, e tutte le Parti saranno obbligate a completare il proprio incarico e le obbligazioni conferite dal presente Accordo entro le date prorogate o come diversamente convenuto per iscritto tra le Parti.

ARTICOLO 4 – OBBLIGAZIONI DELL'ISTITUZIONE

4.1 Rispetto delle regole e delle normative riguardanti gli studi epidemiologici

4.1.1 Durante l'esecuzione dei Servizi, l'ISTITUZIONE si impegna ad osservare ed a garantire che il Coordinatore Scientifico osservi le seguenti normative, regolamentazioni e testi (di seguito i "Testi");

- il Protocollo;
- la Direttiva consolidata 2001/83/CE del Parlamento Europeo e del Consiglio del 6 novembre 2001 sul Codice della Comunità inerente ai prodotti medicinali per uso umano come modificata dalla Direttiva 2002/98/CE, dalla Direttiva 2004/24/CE e dalla Direttiva 2004/27/CE;
- la Dichiarazione di Helsinki adottata nel 1964, comprese le sue successive modificazioni ed integrazioni;
- le Linee Guida Internazionali per una Revisione Etica degli Studi Epidemiologici del Consiglio per le Organizzazioni Internazionali delle Scienze Mediche (CIOMS);
- la Direttiva UE 95/46/EC sulla protezione degli individui in relazione al trattamento dei dati personali, sulla libera circolazione di tali dati e ogni legislazione nazionale di recepimento come il Decreto legislativo italiano n. 196 del 30 giugno 2003;

2003;
- any appropriate procedure provided by SPMSD and/or by the CRO and the Scientific Coordinator;
- the Good Epidemiological Practices (GEP) IEA Guidelines for proper conduct of Epidemiologic Research;
- any other European and/or local laws and regulations applicable to the Study.

Texts may change in their applicable versions during the Study. The Parties expressly agree that the last-dated version of the Texts thereof will be considered to be incorporated by reference in the present Agreement in place of any prior version.

4.1.2 The INSTITUTION undertakes that the Scientific Coordinator shall conduct the Study in compliance with the Texts defined above.

4.2 Description of the Services transferred to the INSTITUTION

4.2.1 The INSTITUTION is appointed by SPMSD to perform the Services which are expressly transferred to it by SPMSD pursuant to the present Agreement.

In accordance with both the Protocol and the list of activities, the INSTITUTION shall perform the Services defined in Annex 2.

The INSTITUTION shall be responsible vis-à-vis SPMSD of the good execution of the Services in terms of quality and compliance with the Calendar and the Texts.

The INSTITUTION shall also have an obligation of professional advice toward SPMSD.

4.2.2 The INSTITUTION shall deal by preference with SPMSD S.N.C. represented by Dr. Laurence Serradell (EPM) and with SPMSD Local Contact, represented by Emilia Perinetti, for any Study local aspects in accordance with a specific communication plan that will be implemented for the Study purpose between SPMSD, the INSTITUTION and SPMSD Local Contact.

4.2.3 Communications in English should be preferential and the Parties expressly agree that all deliverables (such as, but not limited to acts, documents, reports) under this Agreement must be provided to SPMSD in English.

4.2.4 The INSTITUTION shall make the Scientific Coordinator available to conduct the Study within institutional commitment for the

- tutte le opportune procedure fornite da SPMSD e/o dalla CRO e dal Coordinatore Scientifico;
- le Buone Pratiche Epidemiologiche (GEP) e le Linee Guida IEA per l'opportuna conduzione della Ricerca Epidemiologica;
- ogni altra legge e regolamento Europeo e/o nazionale applicabile allo Studio.

I Testi possono subire modifiche nella loro versione applicabile durante lo Studio. Le Parti convengono espressamente che la versione più recente dei Testi sarà considerata incorporata mediante rinvio nel presente Accordo in luogo di ogni altra precedente versione.

4.1.2 L'ISTITUZIONE garantisce che il Coordinatore Scientifico condurrà lo Studio nel rispetto dei Testi sopra menzionati.

4.2 Descrizione dei Servizi affidati all'ISTITUZIONE

4.2.1 L'ISTITUZIONE è incaricata da SPMSD di effettuare i Servizi che le sono espressamente affidati da SPMSD ai sensi del presente Accordo.

L'ISTITUZIONE effettuerà i Servizi definiti nell'Allegato 2 in conformità al Protocollo ed alla lista delle attività.

L'ISTITUZIONE sarà responsabile nei confronti di SPMSD della corretta esecuzione dei Servizi in termini di qualità e di rispetto del Calendario e dei Testi.

L'ISTITUZIONE avrà anche un obbligo di consulenza professionale nei confronti di SPMSD.

4.2.2 L'ISTITUZIONE si relazionerà preferibilmente con SPMSD S.N.C. rappresentata dal Dott. Laurence Serradell (EPM) e con il Contatto Locale di SPMSD, rappresentata da Emilia Perinetti, per ogni aspetto locale dello Studio conformemente ad uno specifico piano di comunicazione che sarà implementato ai fini dello Studio tra SPMSD, l'ISTITUZIONE ed il Contatto Locale di SPMSD.

4.2.3 Le comunicazioni saranno preferibilmente in inglese e le Parti convengono espressamente che tutto il materiale (come, ma non solo, atti, documenti e relazioni) nell'ambito del presente Accordo sarà fornito a SPMSD in inglese.

4.2.4 L'STITUZIONE farà sì che il Coordinatore Scientifico sia disponibile a condurre lo Studio nell'ambito dei compiti istituzionali in riferimento

performance of the activities during the Study. SPMSD will request Services when needed and the INSTITUTION agrees to employ its best efforts to meet such requests. The INSTITUTION undertakes to provide to the Scientific Coordinator with premises equipped with necessary materials to fulfill the Study objectives during the whole course of the Study, at the address mentioned on the first page above.

For the good performance of the Study monitoring, the INSTITUTION undertakes to and is responsible for :

- receive the ERAs appointed by SPMSD in the premises where the Study Services are conducted;
- give to the ERAs appointed by SPMSD a direct access to the source documents and to the Study database

4.3 Description of the Services transferred to the Scientific Coordinator

4.3.1 SPMSD assigns to the Scientific Coordinator, who accepts, a mission of expertise as defined below. The Scientific Coordinator's activities and responsibilities within the Study are the following:

- As Scientific Coordinator, coordination of all the personnel (Key Personnel, Central Laboratory personnel, data manager, biostatistician, etc.) based at the INSTITUTION
- Expert advices on the Study design, feasibility and logistic
- Validation of the Study methodology including statistical analysis plan
- Collaboration and participation in the review and validation of all the Study-related documents (hereinafter referred to as "**Study related Documents**") such as but not limited to the Protocol, Participant Form, ICF, Daily reports, etc.
- Review and validation of the Study Results
- Writing of the Study Report in English
- Review of an abstract or manuscript for publication by SPMSD according to the specific publication rules defined in Article 8
- Participating as Scientific Coordinator in face-to-face meetings such as but not limited to Steering Committee, Advisory Board and/or Investigators meetings, and meetings with SPMSD. (hereinafter referred as the "**Meeting(s)**")
- Being in regular contact with SPMSD by phone or email if applicable
- Participating in telephone conferences

all'esecuzione delle attività durante lo Studio.

SPMSD richiederà i Servizi quando necessario e l'ISTITUZIONE accetta di compiere i massimi sforzi per adempiere a tali richieste. L'ISTITUZIONE si impegna a fornire al Coordinatore Scientifico locali equipaggiati con i materiali necessari alla realizzazione degli obiettivi dello Studio durante l'intero svolgimento dello Studio, all'indirizzo indicato nella prima pagina di cui sopra.

Ai fini della corretta esecuzione del monitoraggio dello Studio, l'ISTITUZIONE si impegna a ed è responsabile di:

- ricevere gli ERAs nominati da SPMSD nei locali dove vengono condotti i Servizi dello Studio;
- dare agli ERAs nominati da SPMSD accesso diretto ai documenti originali ed al database dello Studio

4.3 Descrizione dei Servizi affidati al Coordinatore Scientifico

4.3.1 SPMSD affida al Coordinatore Scientifico, che accetta, il seguente ambito di consulenza, come definito qui di seguito. Le attività e le responsabilità del Coordinatore Scientifico nell'ambito dello Studio sono le seguenti:

- In qualità di Coordinatore Scientifico, la coordinazione di tutto il personale (Personale Qualificato, personale del Laboratorio Centrale, data manager, biostatistico, ecc.) che lavora presso l'ISTITUZIONE
- La consulenza sul disegno, sulla fattibilità e sulla logistica dello Studio
- La validazione della metodologia dello Studio compreso il piano di analisi statistica
- La collaborazione e la partecipazione nella revisione e nella validazione di tutti i documenti relativi allo Studio (di seguito "**Documenti relativi allo Studio**") come, ma non solo il Protocollo, il Modulo dei Partecipanti, ICF, le Relazioni Giornaliere, ecc.
- La revisione e la validazione dei Risultati dello Studio
- La redazione della Relazione dello Studio in inglese
- La revisione di un estratto o manoscritto per la pubblicazione da parte di SPMSD secondo le specifiche regole di pubblicazione definite nell'art. 8
- La partecipazione in qualità di Coordinatore Scientifico ad incontri quali, ma non solo, gli incontri del Comitato Operativo, del Consiglio di Sorveglianza e/o gli incontri con gli Sperimentatori, e gli incontri con SPMSD (di seguito definiti "**Incontro(i)**")
- Il contatto regolare con SPMSD per telefono o per e-mail quando necessario
- La partecipazione alle conferenze telefoniche

organized by SPMSD if applicable

- Informing SPMSD of all events, difficulties or problems which might cause a delay in the performance of the Study, to advice SPMSD on measures needed to be taken and to intervene when necessary. The Parties shall meet and discuss in good faith in order to find a solution to carry on the Study.

4.3.2 The Scientific Coordinator is responsible for all the Services detailed in Annex 2, and in particular, for the activities that shall be delegated to the INSTITUTION's Key Personnel.

The Scientific Coordinator shall be in charge of the Central Laboratory activities as mentioned below:

- Developing all the documentation related to Samples such as but not limited to the Laboratory procedure manual, etc and training all INSTITUTION's Key Personnel and ERAs according to to this documentation
- Providing the Centers with all the documentation required for the Study Samples collection
- Management of Samples from reception until HPV results delivery as described in the Protocol and Laboratory procedure manual
- Creating, updating the Study Database with all the HPV tests results performed within the Study and sending of the Study Database to SPMSD
- Identifying a Central Laboratory representative to assist to any necessary Study Meetings and to answer to all the queries asked by SPMSD or the CRO or the Centers by phone or email if applicable
- Being in regular contact with the CRO and the Centers to allow Study data transfer from the Centers to the Central Laboratory and inversely from the Central Laboratory to the Centers.

The Central Laboratory Services are detailed further in Annex 2.

It is expressly agreed between the Parties that the Scientific Coordinator is not in charge of and cannot be responsible for the Study related activities conducted under the LHU responsibility such as but not limited to recruitment delay and recruitment failure.

4.3.3 The Scientific Coordinator undertakes to attend to and participate actively in the Meetings and to be reactive in responding to

organizzate da SPMSD quando necessario

- La comunicazione a SPMSD di tutte le situazioni, difficoltà o problemi che potrebbero causare un ritardo nell'esecuzione dello Studio, in modo da consigliare SPMSD sulle misure necessarie da adottare e intervenire quando necessario. Le Parti si incontreranno e discuteranno in buona fede al fine di trovare una soluzione per la prosecuzione dello Studio.

4.3.2 Il Coordinatore Scientifico è responsabile per tutti i Servizi elencati nell'Allegato 2, e in particolare, delle attività che saranno delegate al Personale Qualificato dell'ISTITUZIONE.

Il Coordinatore Scientifico sarà incaricato delle attività del Laboratorio Centrale di seguito indicate:

- Sviluppare tutta la documentazione relativa ai Campioni come, ma non solo, il manuale delle procedure di Laboratorio, ecc. e formare tutto il Personale Qualificato ed gli ERAs, secondo tale documentazione
- Fornire ai Centri tutta la documentazione richiesta per la raccolta dei Campioni per lo Studio;
- Gestire i Campioni dalla ricezione fino al rilascio dei risultati HPV come descritto nel Protocollo e nel manuale delle procedure di Laboratorio;
- Creare ed aggiornare il Database dello Studio con tutti i risultati dei test HPV effettuati nell'ambito dello Studio e trasmettere il Database dello Studio a SPMSD;
- Individuare un rappresentante del Laboratorio Centrale per assistere ad ogni necessario Incontro riguardante lo Studio e rispondere a tutte le domande poste da SPMSD o dalla CRO o dai Centri per telefono o per e-mail quando necessario;
- Essere in regolare contatto con la CRO e con i Centri per consentire il trasferimento dei dati dello Studio dai Centri al Laboratorio Centrale e viceversa dal Laboratorio Centrale ai Centri.

I Servizi del Laboratorio Centrale sono più dettagliatamente descritti nell'Allegato 2.

È espressamente pattuito tra le Parti che il Coordinatore Scientifico non è incaricato e non può essere responsabile per le attività connesse allo Studio condotte sotto la responsabilità della ASL quali, ma non solo, il ritardo nel reclutamento o il fallimento dello stesso.

4.3.3 Il Coordinatore Scientifico si impegna a prendere parte ed a partecipare attivamente agli Incontri e ad essere sollecito nel rispondere alle richieste di SPMSD per e-mail o per contatto telefonico.

SPMSD inquiries by emails or phone contact.

4.3.4 The Scientific Coordinator undertakes to have the relevant skills and to make use of all her knowledge and expertise during her participation in the Study for performing Services. All the INSTITUTION's Services governed by the present Agreement shall be executed by no other person than the Scientific Coordinator herself intuitu personae.

4.4 **Skills and competences**

The present Agreement is executed in consideration of the Scientific Coordinator's experience.

Key contacts at the INSTITUTION who shall have functions in the Study are the Scientific Coordinator and any persons who have involvement in the Study and who are employees of the INSTITUTION (hereinafter collectively referred to as the "**Key Personnel**").

The INSTITUTION shall make all reasonable efforts to maintain staffing of the Key Personnel at 100% for the duration of the Agreement. Any change in the Key Personnel must respect the following process:

- The INSTITUTION shall inform SPMSD by one (1) month prior written notice regarding a change to any of the Key Personnel, indicating the reasons of such change, except however in the case of death, period of illness which is more than thirty (30) days, corporate restructure, termination without delay of the labour contract where in such instances the INSTITUTION shall notify SPMSD as soon as it becomes aware of such events and at the latest, within one (1) week.
- The INSTITUTION will replace the Key Personnel with personnel with technical qualification equivalent to the previous Key Personnel.
- SPMSD shall have the right to receive the CVs/resumes and training records of the proposed replacements for the Key Personnel
- Replacement personnel, where possible, shall have an overlap period of at least two (2) weeks so that the original Key Personnel can directly take up the training of the replacement for the Study. The costs of the training, if any, shall be borne by the INSTITUTION.

4.3.4 Il Coordinatore Scientifico garantisce di avere le dovute competenze e di far uso di tutte le proprie conoscenze ed expertise durante la sua partecipazione allo Studio per svolgere i Servizi. Tutti i Servizi dell'ISTITUZIONE regolati dal presente Accordo saranno eseguiti da nessun' altra persona fuorchè dal Coordinatore Scientifico stesso *intuitu personae*.

4.4 **Capacità e competenze**

Il presente Accordo è eseguito in considerazione dell'esperienza del Coordinatore Scientifico.

I contatti fondamentali presso l'ISTITUZIONE che svolgeranno delle funzioni in riferimento allo Studio sono il Coordinatore Scientifico e tutte le persone che sono coinvolte nello Studio e che sono dipendenti dell'ISTITUZIONE (di seguito collettivamente indicate come "**Personale Qualificato**").

L'ISTITUZIONE farà ogni ragionevole sforzo al fine di mantenere lo staff del Personale Qualificato al 100% per tutta la durata dell'Accordo. Qualsiasi sostituzione del Personale Qualificato dovrà rispettare la seguente procedura:

- L'ISTITUZIONE informerà SPMSD con un preavviso scritto di un (1) mese relativamente alla sostituzione di qualsiasi membro del Personale Qualificato, indicando le ragioni di tale sostituzione, ad eccezione delle ipotesi di morte, periodi di malattia superiori a trenta (30) giorni, ristrutturazione aziendale, cessazione senza ritardo del contratto di lavoro, nei quali casi l'ISTITUZIONE notificherà a SPMSD la ricorrenza di tali eventi non appena divengono di sua conoscenza ed al più tardi entro una (1) settimana.
- L'ISTITUZIONE sostituirà il Personale Qualificato con personale con qualificazione tecnica equivalente al precedente Personale Qualificato.
- SPMSD avrà il diritto di visionare i CV e la documentazione inerente la formazione dei sostituti proposti per il Personale Qualificato.
- La sostituzione del personale, quando possibile, avverrà con un periodo di affiancamento di almeno due (2) settimane in modo tale che l'originario Personale Qualificato possa direttamente prendersi carico della formazione dei sostituti per lo Studio. I costi per la formazione, qualora vi siano, saranno sostenuti dall'ISTITUZIONE.

4.5 Subcontracting activities – Delegation of performance

4.5.1 The Parties expressly acknowledge that no delegation of performance under this Agreement is foreseen by the INSTITUTION.

4.5.2 Before any delegation, the INSTITUTION undertakes to inform SPMSD by writing. In case of delegation, the INSTITUTION and/ or the Scientific Coordinator remain liable for the performance it delegated under this Agreement.

4.6 Data protection

Under the terms of the present Agreement, **"Processing"** means the collection, use, transfer, storage, deletion, processing (both by computer and manually), combination or other use of personal data as contemplated by any applicable data protection laws.

"Personal Data" means any data relating to an identified or identifiable natural person.

"Study Data" means all data received or collected during the Study by the INSTITUTION pursuant to the Services provided by the INSTITUTION and the Scientific Coordinator (including the Key Personnel) under this Agreement but excludes Personal Data of the INSTITUTION's own employees and agents such as the Personal Data of the Scientific Coordinator and of any member of the Key Personnel. Nothing contained in the Agreement or otherwise constitutes an acknowledgement that any Study Data maintained actually identifies or could be used to identify a Participant.

4.6.1 The INSTITUTION agrees to comply with all applicable privacy laws and regulations such as the EU Data Protection Directive 95/46/EC (the **"Directive"**) and any local laws. The INSTITUTION agrees, if necessary, to notify its Processing activities under the present Agreement to the supervisory authority and further, shall take any other steps requested by SPMSD, in order to enable SPMSD to comply with any notification or other obligations applicable to SPMSD or its Parent and/or Subsidiary Companies under such laws. The Parties acknowledge that SPMSD is the Data Controller (as defined in the Directive) and the INSTITUTION is a Processor (as defined in the Directive) with respect to the Processing of the Study Data relating to the Services provided under this Agreement.

4.5 Attività subappaltate – Servizi delegati

4.5.1 Le Parti riconoscono espressamente che ai sensi del presente Accordo non è prevista alcuna delega di servizi da parte dall'ISTITUZIONE.

4.5.2 Prima di ogni delega, l'ISTITUZIONE si impegna ad informare per iscritto SPMSD. In caso di delega, l'ISTITUZIONE e/o il Coordinatore Scientifico restano responsabili per l'esecuzione dei servizi delegati nell'ambito del presente Accordo.

4.6 Protezione dei dati

Ai sensi del presente Accordo, il termine **"Trattamento"** indica la raccolta, l'uso, il trasferimento, la conservazione, la cancellazione, l'elaborazione (sia informatica che manuale), la combinazione o ogni altro uso di dati personali, come previsto dalla normative applicabile in materia di protezione dei dati personali.

Il termine **"Dati Personali"** indica tutti i dati relativi ad una persona fisica identificata o identificabile.

"Dati dello Studio" indica tutti i dati ricevuti o raccolti durante lo Studio dall'ISTITUZIONE a seguito dei Servizi forniti dall'ISTITUZIONE e dal Coordinatore Scientifico (ivi compreso il Personale Qualificato) nell'ambito del presente Accordo ma esclude i Dati Personali dei dipendenti e degli agenti dell'ISTITUZIONE come i Dati Personali del Coordinatore Scientifico e di tutti i membri del Personale Qualificato. Nulla di quanto contenuto nell'Accordo o altrove costituisce un riconoscimento che il trattamento di alcuno dei Dati dello Studio identifichi o possa essere usato per identificare una Partecipante.

4.6.1 L'ISTITUZIONE accetta di rispettare tutte le leggi e tutti i regolamenti applicabili in materia di privacy come la Direttiva UE 95/46/CE sulla protezione dei dati personali (la **"Direttiva"**) e tutte le normative nazionali. L'ISTITUZIONE accetta, se necessario, di notificare le attività di trattamento dei dati personali di cui al presente Accordo all'Autorità Garante ed inoltre porrà in essere tutto quanto richiesto da SPMSD, al fine di permettere alla stessa di ottemperare a tutte le notifiche o ad altri obblighi richiesti a SPMSD o alle sue società controllanti e/o controllate ai sensi delle predette normative. Le Parti riconoscono che SPMSD è il titolare del trattamento dei Dati (come definito nella Direttiva) e che l'ISTITUZIONE è un responsabile (come definito nella Direttiva) con riferimento al trattamento dei Dati dello Studio relativi ai Servizi condotti ai sensi del presente Accordo.

4.6.2 The INSTITUTION shall comply with all applicable laws, as amended from time to time, with respect to the Processing of the Study Data and with the following provisions:

(a) Ensuring that the Study Data collected by the INSTITUTION is processed only for the purpose of the present Agreement and in accordance with the Protocol or as otherwise instructed in writing from time to time by SPMSD;

(b) Ensuring that the Study Data is not disclosed or transferred to any third party without the prior written consent of SPMSD, except:

(i) as specifically stated in the Agreement, or

(ii) where such disclosure or transfer is required by any applicable law, regulation or supervisory authority, in which case the INSTITUTION shall, wherever possible, notify promptly in writing SPMSD prior to complying with any such request for disclosure or transfer and shall comply with all reasonable directions of SPMSD with respect to such disclosure or transfer.

(c) Ensuring that the Study Data is accurate and, where necessary, kept updated and use best efforts to ensure that any of the Study Data which is inaccurate or incomplete is erased or rectified.

(d) Ensuring that all appropriate technical and organizational measures are taken to protect the Study Data against accidental or unlawful destruction or accidental loss or alteration, or unauthorized disclosure or access and against all other unlawful forms of Processing.

(e) Notifying SPMSD immediately but no later than two (2) working days of any accidental, unlawful or unauthorized uses or disclosures of the Study Data; ensuring that the INSTITUTION refers to SPMSD any communication received from any of the Participants relating to their rights to access, modify or correct their respective Study Data and that it complies with all instructions of SPMSD before responding to such communications, and

(f) Complying with the terms of the present Agreement and all reasonable instructions of SPMSD to return, store or destroy the Study Data.

4.6.2 L'ISTITUZIONE osserverà tutte le leggi applicabili, come di volta in volta integrate/modificate, relativamente al trattamento dei Dati dello Studio e le seguenti prescrizioni:

(a) Assicurare che i Dati dello Studio raccolti dall'ISTITUZIONE siano trattati esclusivamente per le finalità del presente Accordo e nel rispetto del Protocollo o secondo le istruzioni fornite di volta in volta per iscritto da SPMSD;

(b) Assicurare che i Dati dello Studio non siano diffusi o trasferiti a terzi senza il previo consenso scritto di SPMSD, salvo se:

(i) specificamente previsto nell'Accordo, o

(ii) nel caso in cui tale divulgazione o trasferimento sia richiesto da una legge o un regolamento applicabile o dall'Autorità Garante, nel qual caso l'ISTITUZIONE, ove possibile, informerà prontamente per iscritto SPMSD prima di ottemperare a tali richieste di divulgazione o trasferimento e si conformerà a tutte le ragionevoli istruzioni di SPMSD in merito alla predetta divulgazione o trasferimento.

(c) Assicurare che i Dati dello Studio siano accurati e, ove necessario, mantenuti aggiornati e fare il massimo sforzo per assicurare che tutti i Dati dello Studio che risultassero inesatti o incompleti siano cancellati o rettificati.

(d) Assicurare che vengano adottate tutte le più appropriate misure tecniche ed organizzative per proteggere i Dati dello Studio contro distruzioni accidentali o illecite, o perdite o alterazioni accidentali, o divulgazioni o accessi non autorizzati e contro ogni ulteriore forma di trattamento illecito.

(e) Informare SPMSD immediatamente ma non più tardi di due (2) giorni lavorativi in merito ad ogni uso o divulgazione accidentale, illecita o non autorizzata dei Dati dello Studio; assicurare che l'ISTITUZIONE informi SPMSD in merito ad ogni comunicazione ricevuta da qualsivoglia Partecipante in merito al loro diritto di accedere, modificare o correggere i rispettivi Dati dello Studio e che essa osservi le istruzioni di SPMSD prima di rispondere a tali comunicazioni, e

(f) Osservare tutte le prescrizioni di cui al presente Accordo e tutte le ragionevoli istruzioni di SPMSD in ordine alla restituzione, conservazione o distruzione dei Dati dello

Studio.

4.6.3 The INSTITUTION and the Scientific Coordinator recognizes that certain Personal Data with respect to the Key Personnel are processed for the purposes of (i) Study management in SPMSD databases and (ii) making them available to national, foreign and/or international authorities, organizations specialized in the supervision, audit and control of biomedical researches. The collected Personal Data may be subject to transfer outside the European Union in order to be made available to companies from SPMSD's group, SPMSD service providers/vendors and/or ethics committees, health or regulatory agencies.

4.6.3 L'ISTITUZIONE ed il Coordinatore Scientifico riconoscono che alcuni Dati relativi al Personale Qualificato sono trattati al fine (i) della gestione dello Studio nelle banche dati di SPMSD e (ii) di renderli disponibili alle autorità nazionali, estere e/o internazionali, alle organizzazioni specializzate nella supervisione, negli audit e nel controllo delle ricerche biomediche. I Dati Personali raccolti possono essere soggetti a trasferimenti al di fuori dell'Unione Europea al fine di renderli disponibili alle società del gruppo SPMSD, fornitori di servizi di SPMSD e/o comitati etici, autorità sanitarie o regolatorie.

4.6.4 According to the French Act n° 78-17 of 6 January 1978 on Data Processing, Data Files and Individual Liberties (as amended by the Act of 6 August 2004 relating to the Protection of Individuals with regards to the Processing of Personal Data and by the Act of 12 May 2009 relating to the simplification and clarification of law and lightening of procedures), SPMSD informs the INSTITUTION that the Scientific Coordinator and each member of the Key Personnel has the right to access to and correct his/her Personal Data by sending a written request to Sanofi Pasteur MSD SNC – Epidemiological Department Europe - 8, rue Jonas Salk 69367 Lyon Cedex 07 FRANCE.

4.6.4 Ai sensi della Legge Francese n° 78-17 del 6 Gennaio 1978 su Trattamento dei dati, File Dati e Libertà Individuali (come modificata dall'Atto del 6 agosto 2004 relativo alla protezione degli individui in riferimento al trattamento dei dati personali e dall'Atto del 12 maggio 2009 relativo alla semplificazione e chiarificazione delle leggi e allo snellimento delle procedure), SPMSD informa l'ISTITUZIONE che il Coordinatore Scientifico ed ogni membro del Personale Qualificato hanno il diritto di accedere e correggere i propri Dati Personali inviando richiesta scritta a Sanofi Pasteur MSD SNC – Epidemiological Department Europe - 8, rue Jonas Salk 69367 Lyon Cedex 07 FRANCE.

ARTICLE 5 – SPMSD OBLIGATIONS

5.1 As Sponsor of the Study, SPMSD shall abide by the Texts and assume all other duties and tasks that are not transferred to the INSTITUTION by virtue of the present Agreement.

5.2 Additionally SPMSD agrees to provide the INSTITUTION with all information (such as without limitation, regulatory documents, administrative documents, Study-related Documents, etc.), the knowledge of which is deemed necessary to implement the Study, whether this information is technical data or the rationale for carrying out the missions required by SPMSD as Sponsor.

5.3 SPMSD shall also provide the INSTITUTION with any revisions or changes in known data that could have an impact on the performance of the Study.

ARTICOLO 5 – OBBLIGHI DI SPMSD

5.1 In qualità di Promotore dello Studio, SPMSD dovrà rispettare i Testi ed assumere tutti gli altri obblighi ed impegni che non sono trasferiti all'ISTITUZIONE per effetto del presente Accordo.

5.2 Inoltre SPMSD accetta di fornire all'ISTITUZIONE tutte le informazioni (quali, senza limitazioni, documenti regolatori, documenti amministrativi, Documenti relativi allo Studio, ecc.), la cui conoscenza è ritenuta necessaria ai fini della conduzione dello Studio, sia che tali informazioni si riferiscano a dati tecnici sia che essi rappresentino il razionale per l'esecuzione delle prestazioni richieste da SPMSD come Promotore.

5.3 SPMSD si impegna inoltre a fornire all'ISTITUZIONE tutte le revisioni o modifiche relative ai dati conosciuti che possano avere un impatto sull'esecuzione dello Studio.

ARTICLE 6 - FINANCIAL PROVISIONS

6.1 In consideration for performing the Services and the INSTITUTION's obligations under this Agreement, SPMSD shall pay the INSTITUTION fees that amount to 880 770 euros (eight Thousand eighty and seven hundred seventy)exclusive of VAT (hereinafter referred to as the "**Budget**"). Financial provisions with payment modalities and payment terms are detailed in Annex 2.

6.2 All travel, accommodation and catering expenses incurred by the Scientific Coordinator and/or other ISPO Key Personnel in the course of the Services which are reasonable and accessory to the said Services (in compliance with the Directive 21/83/EC on the Community code relating to medicinal products for human use) and which will be authorized by SPMSD in writing in advance shall be born by SPMSD through the services of a travel agency that will invoice directly SPMSD.

6.3 All payments due under this Agreement will be made by SPMSD to the INSTITUTION by bank transfer/bearer cheque within 30 (thirty) days end of month from the date of sending of the invoice.

6.4 The INSTITUTION (the Scientific Coordinator or other ISPO Key Personnel) is not entitled to request from SPMSD any financial contribution for participation of the Scientific Coordinator in congress, symposia, meetings etc. without SPMSD prior written consent.

6.5 The above-mentioned payments are full and complete compensation for all the Services provided, and obligations assumed by the INSTITUTION under this Agreement.

6.6 The Parties acknowledge that the financial provisions are agreed between the Parties taking into account the Services as defined in article 4.2 and Annex 2 at the date of signature of the present Agreement. Any amendment to these financial provisions shall be discussed in good faith between the Parties.

All requests to review the financial provisions shall be reasonable and shall have to be justified by the INSTITUTION and the Scientific Coordinator. Accordingly, SPMSD commits itself to review such financial consideration. Any modification made to the financial provisions shall be subject to the signature of an amendment to this Agreement duly executed by the representatives of the Parties as defined in article 13.6 of the present Agreement. If the Parties fail to agree on the

ARTICOLO 6 – DISPOSIZIONI FINANZIARIE

6.1 Per l'esecuzione dei Servizi e degli obblighi dell'ISTITUZIONE ai sensi del presente Accordo, SPMSD verserà all'ISTUTUZIONE un corrispettivo pari a 880.770 Euro (ottocentottantamila settecentosettanta) IVA esclusa (di seguito il "**Budget**"). Le disposizioni finanziarie con le modalità ed i termini di pagamento sono dettagliatamente esposte nell'Allegato 2.

6.2 Tutte le spese di viaggio, soggiorno e vitto sostenute dal Coordinatore Scientifico e/o da altro Personale Qualificato di ISPO nel corso dei Servizi che siano ragionevoli ed accessorie ai Servizi anzidetti (in conformità alla Direttiva 21/83/CE sul codice comunitario relativo ai prodotti medicinali per uso umano) e che saranno preventivamente autorizzate per iscritto da SPMSD saranno sostenute da quest'ultima attraverso una agenzia viaggi che fatturerà direttamente a SPMSD.

6.3 Tutti i pagamenti dovuti ai sensi del presente Accordo saranno effettuati da SPMSD a favore dell'ISTITUZIONE mediante bonifico bancario/assegno al portatore entro (30) trenta giorni data fine mese dalla data di invio della fattura.

6.4 L'ISTITUZIONE (il Coordinatore Scientifico o altro Personale Qualificato di ISPO) non ha diritto di richiedere a SPMSD qualsivoglia contributo finanziario per la partecipazione del Coordinatore Scientifico a congressi, convegni, incontri ecc., senza il preventivo consenso scritto di SPMSD.

6.5 I sopra menzionati pagamenti costituiscono il corrispettivo integrale e complessivo per tutti i Servizi resi e le obbligazioni assunte in virtù del presente Accordo.

6.6 Le Part riconoscono che le disposizioni finanziarie sono concordate tra le Parti prendendo in considerazione i Servizi come definiti nell'articolo 4.2. e nell'Allegato 2 alla data di sottoscrizione del presente Accordo. Qualsiasi modifica alle presenti disposizioni finanziarie sarà discussa in buona fede tra le Parti.

Tutte le richieste di rivedere le disposizioni finanziarie dovranno essere ragionevoli e dovranno essere motivate dall'ISTITUZIONE e dal Coordinatore Scientifico. Di conseguenza, SPMSD si impegna a riesaminare tale corrispettivo finanziario. Ogni modifica effettuata alle disposizioni finanziarie sarà sottoposta alla sottoscrizione di un atto integrativo del presente Accordo debitamente formalizzato dai rappresentanti delle Parti come definite nell'art. 13.6 del presente Accordo. Qualora le Parti non dovessero raggiungere

former, the financial provisions shall continue to apply unless any of the above conditions (Calendar) have changed for reasons not attributable to the INSTITUTION and/or the Scientific Coordinator; in which event the INSTITUTION shall be entitled to recover its reasonable additional costs and expenses.

un accordo, le disposizioni finanziarie continueranno ad essere applicate a meno che una delle sopramenzionate condizioni (Calendario) sia mutata per ragioni non attribuibili all'ISTITUZIONE e/o al Coordinatore Scientifico; nel qual caso l'ISTITUZIONE avrà diritto di recuperare i ragionevoli costi addizionali e le spese da essa sostenute.

ARTICLE 7 - CONFIDENTIALITY

7.1 The INSTITUTION and the Scientific Coordinator agree to keep confidential and to not publish or otherwise disclose to any third party and to not use for any other purpose than the performance of the Study, (i) any information, data and/or Study-related Documents received from SPMSD under the present Agreement or resulting from and/or developed during the Study, (ii) any Study Reports and/or Study Results, in whatever form and by any means whatsoever, without the prior written consent of SPMSD (hereinafter the **"Confidential Information"**). Consequently the INSTITUTION and the Scientific Coordinator undertake to take all necessary measures to safeguard such Confidential Information from access by anyone not authorized in writing by SPMSD. It is acknowledged by the Parties that the INSTITUTION as public institution is committed to provide annually Italian authorities with information on their activities. It is agreed that general or public known information related to the Study could be disclosed except unpublished Study Results.

ARTICOLO 7 - RISERVATEZZA

7.1 L'ISTITUZIONE ed il Coordinatore Scientifico concordano di mantenere confidenziale e di non pubblicare o divulgare in altro modo a terze parti e di non usare per scopi diversi dall'esecuzione dello Studio, (i) qualsiasi informazione, dato e/o Documento relativo allo Studio ricevuto da SPMSD ai sensi del presente Accordo o risultante da e/o sviluppato durante lo Studio, (ii) qualsivoglia Relazione dello Studio e/o Risultati dello Studio in qualunque forma e modo, senza il previo consenso scritto di SPMSD (di seguito **"Informazioni Riservate"**). Conseguentemente l'ISTITUZIONE ed il Coordinatore Scientifico si impegnano ad adottare tutte le misure necessarie per tutelare tali Informazioni Riservate dall'accesso di chiunque non sia autorizzato per iscritto da SPMSD. È riconosciuto dalle Parti che l'ISTITUZIONE quale pubblica istituzione è tenuta ad informare annualmente le autorità italiane in merito alle sue attività. Si conviene che le informazioni generalmente o pubblicamente conosciute relative allo Studio possono essere divulgate ad eccezione dei Risultati non pubblicati dello Studio.

7.2 The INSTITUTION and the Scientific Coordinator undertake and shall ensure by any means that its employees and in particular the Key Personnel, associates, and/or directors, agents, consultants, if any who may intervene in the performance of the Services within the Study respect the above confidentiality obligation. The INSTITUTION and the Scientific Coordinator shall be responsible towards SPMSD for non-compliance with the aforesaid provisions by those persons.

7.2 l'ISTITUZIONE ed il Coordinatore Scientifico si impegnano ed assicurano con ogni mezzo che i propri dipendenti ed in particolare il Personale Qualificato, gli associati e/o i direttori, gli agenti, i consulenti, qualora intervengano nell'esecuzione dei Servizi nell'ambito dello Studio rispettino gli obblighi di riservatezza sopra indicati. L'ISTITUZIONE ed il Coordinatore Scientifico saranno responsabili nei confronti di SPMSD del mancato rispetto delle presenti disposizioni da parte di tali soggetti..

7.3 Provided that the INSTITUTION and the Scientific Coordinator can give written evidence, the obligations under the present article shall not apply to:

(i) information generally known to the public, provided this occurs by means other than the breach of this Agreement by the INSTITUTION, its employees and in particular the Key Personnal and/or the Scientific Coordinator,

7.3 Purchè l'ISTITUZIONE ed il Coordinatore Scientifico possano fornirne prova scritta, gli obblighi di cui al presente articolo non si applicheranno a:

(i) Informazioni di dominio pubblico, purchè ciò non derivi dall'inadempimento del presente Accordo da parte dell'ISTITUZIONE, dei suoi dipendenti ed in particolare del Personale Qualificato e/o del Coordinatore Scientifico, degli associati e/o dei direttori, ove ve ne siano.

associates, and/or directors if any,

(ii) information with which SPMSD agreed in writing, that was available to the INSTITUTION and/or to the Scientific Coordinator on a non-confidential basis prior to its disclosure to the INSTITUTION and/or to the Scientific Coordinator, or that was communicated by the INSTITUTION and/or the Scientific Coordinator to a designated third party on the express request of SPMSD,

(iii) information which became or becomes available to the INSTITUTION and/or to the Scientific Coordinator on a non-confidential basis from a source other than SPMSD, provided that such source is not under an obligation of confidentiality concerning that information to the INSTITUTION and/or to the Scientific Coordinator or SPMSD or any other person or entity.

Furthermore, the INSTITUTION and the Scientific Coordinator shall be authorized to disclose Confidential Information when it is legally required by a public authority or a local regulatory body, *provided however*, that the INSTITUTION and the Scientific Coordinator shall (i) notify SPMSD previously in writing of such disclosure, (ii) inform SPMSD of the nature of the Confidential Information disclosed and (iii) guarantee that such disclosed Confidential Information will remain confidential for all other purposes.

7.4 It may become necessary for the INSTITUTION and for the Scientific Coordinator to disclose to SPMSD information which the INSTITUTION and the Scientific Coordinator consider proprietary, privileged and confidential (hereinafter the **"INSTITUTION and/or the Scientific Coordinator's Confidential Information"**). If disclosure of the INSTITUTION and/or the Scientific Coordinator's Confidential Information occurs, then SPMSD agrees to protect the INSTITUTION and/or the Scientific Coordinator's Confidential Information as confidential with same degree of care as SPMSD would protect its own confidential information and will not use such information for any motive other than the purpose of the present Agreement.

7.5 This secrecy obligation shall remain in full force and effect for a period of fifteen (15) years following expiration or otherwise termination of the present Agreement, for

(ii) Informazioni in merito alle quali SPMSD ha convenuto per iscritto che erano rese disponibili all'ISTITUZIONE e/o al Coordinatore Scientifico in via non riservata precedentemente alla loro divulgazione all'ISTITUZIONE e/o al Coordinatore Scientifico, o che erano comunicate dall'ISTITUZIONE e/o dal Coordinatore Scientifico a terzi su espressa richiesta di SPMSD,

(iii) Informazioni che sono diventate o divengono disponibili all'ISTITUZIONE e/o al Coordinatore Scientifico in via non riservata da altra fonte rispetto a SPMSD, purchè tale fonte non sia vincolata all'obbligo di riservatezza con riferimento a quella informazione nei confronti dell'ISTITUZIONE e/o del Coordinatore Scientifico o di SPMSD o di qualunque altro soggetto.

Inoltre, l'ISTITUZIONE ed il Coordinatore Scientifico saranno autorizzati a divulgare le Informazioni Riservate quando sia legalmente richiesto da una pubblica autorità o da altro ente regolatorio locale, *purchè in ogni caso* l'ISTITUZIONE ed il Coordinatore Scientifico (i) informino preventivamente per iscritto SPMSD di tale divulgazione, (ii) informino SPMSD della natura delle Informazioni Riservate divulgate e (iii) garantiscano che tali Informazioni Riservate divulgate rimarranno confidenziali per ogni altro scopo.

7.4 Potrebbe essere necessario per l'ISTITUZIONE e per il Coordinatore Scientifico comunicare a SPMSD informazioni che l'ISTITUZIONE e il Coordinatore Scientifico considerano di proprietà, privilegiate e riservate (di seguito le **"Informazioni Riservate dell'ISTITUZIONE e/o del Coordinatore Scientifico"**). In caso di comunicazioni riguardanti le Informazioni Riservate dell'ISTITUZIONE e/o del Coordinatore Scientifico, SPMSD accetta di tutelare le informazioni Riservate dell'ISTITUZIONE e/o del Coordinatore Scientifico come riservate con lo stesso grado di cura con cui SPMSD tutelerebbe le proprie informazioni riservate e di non usare tali informazioni per motivi diversi dallo scopo del presente Accordo.

7.5 Il presente obbligo di riservatezza rimarrà valido ed efficace per un periodo di quindici (15) anni dalla scadenza o altra eventuale cessazione del presente Accordo, per qualsivoglia motivo.

whatever reason.

ARTICLE 8 - PROPERTY – PUBLICATION RULES – USE OF THE STUDY REPORTS

8.1 Property

8.1.1 Property of SPMSD's Confidential Information and Study-related Documents

Pursuant to Article 7 and notwithstanding anything contrary to section 7.4 above, it is expressly agreed upon between the Parties that any and all the Confidential Information shall be and remain the exclusive property of SPMSD. Therefore the INSTITUTION and the Scientific Coordinator expressly agree that this Agreement shall not be construed as conferring or granting any intellectual property rights or any license to the INSTITUTION and/or the Scientific Coordinator pertaining to SPMSD's Confidential Information, either express or implied.

8.1.2 Property of the INSTITUTION and the Scientific Coordinator's Confidential Information

Notwithstanding the foregoing, it is expressly agreed upon between the Parties that any and all the INSTITUTION and/or the Scientific Coordinator's Confidential Information shall be and remain the exclusive property of the INSTITUTION and/or the Scientific Coordinator.

8.1.3 Ownership of the Study Database

The INSTITUTION and the Scientific Coordinator warrant to SPMSD that the Study Database and Results shall not knowingly infringe any intellectual property rights of any third party.

SPMSD, as Sponsor of the Study, shall be and remain the exclusive owner of the Study Database and Results. SPMSD shall be free to use them by any means in accordance with the Protocol.

Notwithstanding the foregoing, SPMSD hereby grants the Scientific Coordinator a limited, non-exclusive and non sub-licensable, royalty-free, license solely as necessary for the Scientific Coordinator to use the Study Results for publication and communication purposes under the conditions of article 8.2 below.

ARTICOLO 8 – PROPRIETA' – REGOLE DI PUBBLICAZIONE – USO DELLE RELAZIONI DELLO STUDIO

8.1 Proprietà

8.1.1 Proprietà delle Informazioni Riservate di SPMSD e dei Documenti relativi allo Studio

Ai sensi dell'art. 7 e nonostante quanto diversamente disposto nel precedente art. 7.4, è espressamente convenuto tra le Parti che tutte le Informazioni Riservate saranno e rimarranno di esclusiva proprietà di SPMSD. Pertanto l'ISTITUZIONE ed il Coordinatore Scientifico concordano espressamente che il presente Accordo non sarà inteso nel senso di conferire o garantire qualsivoglia diritto di proprietà intellettuale o qualsivoglia licenza all'ISTITUZIONE e/o al Coordinatore Scientifico in riferimento alle Informazione Riservate di SPMSD, sia espressamente che implicitamente.

8.1.2 Proprietà delle Informazioni Riservate dell'ISTITUZIONE e del Coordinatore Scientifico

Nonostante quanto sopra disposto, è espressamente convenuto tra le Parti che tutte le Informazioni Riservate dell'ISTITUZIONE e/o del Coordinatore Scientifico saranno e rimarranno di esclusiva proprietà dell'ISTITUZIONE e/o del Coordinatore Scientifico.

8.1.3 Proprietà del Database dello Studio

L'ISTITUZIONE e il Coordinatore Scientifico garantiscono a SPMSD che il Database dello Studio ed i Risultati dello Studio non violeranno di proposito i diritti di proprietà intellettuale di terzi.

SPMSD, in qualità di Promotore dello Studio, sarà e rimarrà l'esclusivo proprietario del Database dello Studio e dei Risultati dello Studio. SPMSD sarà libero di usarli in qualsiasi modo nel rispetto del Protocollo.

Nonostante quanto sopra esposto, SPMSD con il presente Accordo garantisce al Coordinatore Scientifico una licenza limitata, non esclusiva e non sub licenziabile, senza royalties, unicamente ove necessaria al Coordinatore Scientifico per l'uso dei Risultati dello Studio ai fini della pubblicazione e comunicazione nel rispetto delle condizioni di cui al successivo art. 8.2.

This license is enforceable in all continents and shall be valid for a period of five (5) years from delivery date of the ESR to SPMSD.

One (1) copy of the Study Database shall stay at the Scientific Coordinator's disposal at the end of the Study provided that the Scientific Coordinator shall not exploit commercially or not, modify, decompile, or disassemble the Study Database which shall be treated as SPMSD's Confidential Information under Article 7.

8.2 Publication and communication rules

8.2.1 For any publication and communication contemplated by either SPMSD, the Scientific Coordinator or the Coordinating Investigators (hereinafter the "**Publishing Party**"), a draft in whatever form (manuscript, abstract, posters or any other materials) (hereinafter to as the "**Draft**") must be received by the other parties (hereinafter the "**Receiving Parties**") for the purpose of allowing the Receiving Parties to comment on the contemplated draft and to ensure that the Study Results are accurately reported, have not been misrepresented, and that confidentiality and intellectual property rights have not been breached. It is expressly agreed by both Parties that manuscripts should meet the requirements of the international guidelines (http://www.icmje.org) edited by the International Committee of Medical Journal Editors (ICMJE). The authorship will be decided between the Parties and in any case the contribution of the Scientific Coordinator shall be at least the last Author for the first publication.

8.2.2 The Receiving Parties shall have a period of thirty (30) working days to review the contemplated Draft, have reservations if any, and formulate their acceptance or refusal in whole or in part.

8.2.3 If all the Receiving Parties agree with the Draft, the Receiving Parties shall confirm it by writing to the Publishing Party. The final Draft shall then be submitted to the appropriate committee (congress, peer-reviewed journal, etc.).

8.2.4 If any of the Receiving Parties formulates any reservation on the submitted Draft, the Publishing Party undertakes to delete or modify the Draft according to the directives of the Receiving Parties. The Publishing Party shall submit to the Receiving Parties the final Draft. The Receiving Parties shall have a period of thirty (30) working days to review the final Draft. If the Receiving Parties agree with the

Tale licenza è efficace in tutti i continenti e avrà validità per un periodo di cinque (5) anni dalla data di consegna della Relazione dello Studio Epidemiologico a SPMSD.

Una (1) copia del Database dello Studio rimarrà a disposizione del Coordinatore Scientifico al termine dello Studio purchè il Coordinatore Scientifico non sfrutti commercialmente o in altro modo, non modifichi, cancelli o scomponga il Database dello Studio che dovrà essere trattato al pari delle Informazioni Riservate di SPMSD ai sensi dell'art. 7.

8.2 Regole di pubblicazione e diffusione

8.2.1 Per qualsiasi pubblicazione e comunicazione prevista rispettivamente da SPMSD, dal Coordinatore Scientifico o dagli Sperimentatori Coordinatori (di seguito la "**Parte Pubblicante**"), dovrà essere fornita alle altre parti (di seguito le "**Parti Riceventi**") una bozza in qualsiasi forma (manoscritto, estratto, poster o ogni altro materiale) (di seguito la "**Bozza**") allo scopo di permettere alle Parti Riceventi di esprimere i propri commenti in merito a tale bozza e di assicurare che i Risultati dello Studio siano riportati correttamente e non siano rappresentati erroneamente, e che i diritti di riservatezza e di proprietà intellettuale non siano stati violati. È espressamente convenuto da entrambe le Parti che i manoscritti si dovranno conformare alle linee guida internazionali (http://www.icmje.org) emanate dal Comitato Internazionale degli Editori delle Riviste Mediche (ICMJE). La paternità della pubblicazione sarà decisa tra le Parti ed in ogni caso il contributo del Coordinatore Scientifico sarà rappresentato almeno come ultimo Autore della prima pubblicazione.

8.2.2 Le Parti Riceventi avranno un periodo di trenta (30) giorni lavorativi per rivedere la menzionata Bozza, esprimere eventuali riserve e formulare la propria accettazione o il rifiuto in tutto o in parte.

8.2.3 Qualora le Parti Riceventi concordino sulla Bozza, esse lo confermeranno per iscritto alla Parte Pubblicante. La Bozza Finale sarà quindi trasmessa alla competente commissione (congresso, rivista scientifica paritaria ecc.).

8.2.4 Qualora una delle Parti Riceventi formuli una qualsiasi riserva sulla Bozza trasmessa, la Parte Pubblicante si impegna a cancellare o modificare la Bozza secondo le direttive delle Parti Riceventi. La Parte Pubblicante sottoporrà alle Parti Riceventi la Bozza Finale. Le Parti Riceventi avranno un periodo di trenta (30) giorni lavorativi per revisionare la Bozza Finale. Se le Parti Riceventi concordano con la Bozza Finale proposta dalla Parte Pubblicante, la

final Draft proposed by the Publishing Party, the final Draft shall be submitted to the appropriate committee (congress, peer-reviewed journal, etc.).

Bozza finale sarà trasmessa alla competente commissione (congresso, rivista scientifica paritaria ecc.).

8.2.5 If one of or all the Receiving Party disagree on the submitted or final Draft, the Parties shall meet for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement. If necessary the Study Advisory Board will be consulted. The Publishing Party agrees not to release the said Draft until such time as a resolution has been reached.

8.2.5 Qualora una o tutte le Parti Riceventi non concordino sulla Bozza finale trasmessa, le Parti si incontreranno al fine di discutere insieme e fare in modo di risolvere in buona fede qualsiasi controversia o disaccordo. Ove necessario sarà consultato il Consiglio di Sorveglianza dello Studio. La Parte Pubblicante accetta di non pubblicare la predetta Bozza finchè non sia stata trovata una soluzione.

8.2.6 If no response is received by the Publishing Party from the Receiving Parties on either the submitted or final Draft, it may be conclusively presumed that the Receiving Parties have no objection to the proposed publication that shall be submitted to a peer-review journal before publication.

8.2.6 Qualora la Parte Pubblicante non riceva alcuna riposta dalle Parti Riceventi in merito alla Bozza trasmessa o alla Bozza Finale, si potrà conclusivamente presumere che le Parti Riceventi non abbiano nessuna obiezione sulla proposta pubblicazione che sarà trasmessa ad una rivista scientifica sottoposta a revisione paritaria prima della pubblicazione.

8.2.7 The Parties expressly agree that the first publication on the Study Results shall be retained by SPMSD. SPMSD will draft the manuscript within six (6) months after receiving the final report by the Scientific Coordinator. The Scientific Coordinator and the Coordinating Investigators shall have the opportunity to participate in this first publication disseminating the Study Results. The authorship, between people involved in the Study group, will be decided between the Parties as soon as the final Study Results are available. In any case, the contribution of the Scientific Coordinator shall be at least the last author in this first publication. The contribution of the other ISPO Key Personnel shall be recognised in this first publication by co-authorship if their contributions meet the ICMJE publication rules.

8.2.7 Le Parti convengono espressamente che la prima pubblicazione dei Risultati dello Studio sarà assicurata a SPMSD. Essa redigerà il manoscritto entro sei (6) mesi dalla ricezione della relazione finale dal Coordinatore Scientifico. Il Coordinatore Scientifico e gli Sperimentatori Coordinatori avranno l'opportunità di partecipare a tale prima pubblicazione sui Risultati dello Studio. La titolarità della paternità, tra i soggetti coinvolti nel gruppo dello Studio, sarà concordata tra le Parti non appena i Risultati dello Studio saranno disponibili. In ogni caso, il contributo del Coordinatore Scientifico sarà rappresentato almeno come ultimo Autore della prima pubblicazione. La collaborazione dell'altro Personale Qualificato dell'ISPO sarà riconosciuta in questa prima pubblicazione come co-autori se i loro contributi si conformano alle regole di pubblicazione dell'ICMJE.

8.2.8 Presentation/Communication
Any presentation or communication contemplated by either the Scientific Coordinator and/or the INSTITUTION shall be approved by SPMSD beforehand.

8.2.8 Presentazione/Comunicazione
Qualsiasi presentazione o comunicazione prevista ripettivamente dal Coordinatore Scientifico e/o dall'ISTITUZIONE dovrà essere approvata preventivamente da SPMSD.

8.3 Use of and copyrights on the Study Reports

The Scientific Coordinator expressly acknowledges that any and all the Study Reports (defined in Article 1 above) belong solely and exclusively to SPMSD who shall be free to use and utilize them by any means, in accordance with the Protocol, and to make publication and/or presentation and, in particular, to disclose them to any health authorities.

8.3 Uso delle Relazioni dello Studio e relativi diritti d'autore

Il Coordinatore Scientifico riconosce espressamente che ciascuna e tutte le Relazioni dello Studio (definite nel precedente art. 1) appartengono unicamente ed esclusivamente a SPMSD la quale sarà libera di usarle ed utilizzarle in ogni modo, in conformità al Protocollo, e di farne oggetto di pubblicazioni e/o presentazioni e, in particolare, di rivelarle a qualsiasi autorità sanitaria.

To this end, all property rights relating to future use and representation related to the Study Reports, as well as copyrights related to the latter (with no prejudice to the moral rights belonging to their authors) shall be freely assigned and transferred to SPMSD.

In the case SPMSD decide to publish or to make any presentation of the Study Reports, SPMSD undertakes that such publication and/or presentation will reflect the contribution of the Scientific Coordinator, as last author in the authorship when applicable.

A tal fine, tutti i diritti di proprietà relativi ai futuri usi e rappresentazioni relativi alle Relazioni dello Studio, come i diritti di autore riguardanti queste ultime (senza alcun pregiudizio dei diritti morali appartenenti ai relativi autori) saranno liberamente attribuiti e trasferiti a SPMSD.

Nel caso in cui SPMSD decida di pubblicare o effettuare una presentazione delle Relazioni dello Studio, SPMSD garantisce che tale pubblicazione e/o presentazione rifletterà il contributo del Coordinatore Scientifico, come autore finale in relazione alla paternità, ove applicabile.

ARTICLE 9 – AUDITS AND INSPECTIONS

9.1 Audits - General considerations

Audits may be conducted by SPMSD or by external auditors duly appointed by SPMSD in the INSTITUTION premises/offices during the opening hours in order to ensure that the Services are carried out in compliance with the provisions of the present Agreement and in particular the Texts. Audits may be conducted as long as SPMSD will use the Study Results.

Prior to the conduct of any audit, all external auditors appointed by SPMSD shall execute and agree to be bound by a confidentiality agreement that is at least as restrictive as the provisions of article 7 hereof for the benefit of the INSTITUTION.

SPMSD shall inform the INSTITUTION with a thirty (30) calendar-day prior written notice with before conduction of any audit. In case of 'for cause audit' SPMSD may perform the audit upon a shorter notice.

To this end, the INSTITUTION shall ensure that SPMSD or the external auditors duly appointed by SPMSD shall:

- have access to the INSTITUTION's premises/offices;
- have access to any and all Study information and Study-related Documents;
- meet and have interview with any person involved in the performance of the Services and in particular with the Key Personnel.

Following the audits, the INSTITUTION undertakes to take into account all observations/written comments made by SPMSD and/or the external auditors duly appointed by SPMSD, and to implement promptly any corrective actions necessary for

ARTICOLO 9 – AUDIT ED ISPEZIONI

9.1 Audit – Considerazioni Generali

Gli Audit potranno essere condotti da SPMSD o da auditor esterni debitamente nominati da SPMSD nei locali/uffici dell'ISTITUZIONE durante l'orario di apertura di tali strutture al fine di assicurare che i Servizi siano eseguiti nel rispetto delle prescrizioni del presente Accordo ed in particolare nel rispetto dei Testi. Gli Audit potranno essere condotti fintanto che SPMSD userà i Risultati dello Studio.

Prima dello svolgimento di qualsiasi audit, tutti gli auditor esterni nominati da SPMSD dovranno eseguire ed accettare di essere vincolati ad un accordo di riservatezza che sia restrittivo almeno quanto le disposizioni di cui al precedente art. 7 a beneficio dell'ISTIUZIONE.

SPMSD informerà l'ISTITUZIONE con un preavviso scritto di trenta (30) giorni di calendario prima dello svolgimento di ciascun audit. In caso di 'audit motivato' SPMSD potrà effettuare il controllo con un preavviso più breve.

A tal fine, l'ISTITUZIONE assicurerà che SPMSD o gli auditor esterni debitamente nominati da SPMSD:

- avranno accesso ai locali/uffici dell'ISTITUZIONE;
- avranno accesso a tutte le informazioni dello Studio ed ai Documenti relativi allo Studio;
- incontreranno ed avranno colloqui con tutte le persone coinvolte nell'esecuzione dei Servizi ed in particolare con il Personale Qualificato.

A seguito degli audit, l'ISTITUZIONE si impegna a tener conto di tutte le osservazioni/commenti scritti effettuati da SPMSD e/o dagli auditor esterni debitamente nominati da SPMSD, e ad adottare prontamente tutte le azioni correttive necessarie per la corretta esecuzione dei Servizi nel rispetto delle

the good performance of the Services in compliance with the provisions of the present Agreement and in particular the Texts.

9.2 Financial audits

Upon reasonable prior notification, SPMSD may audit the INSTITUTION in its premises/offices during working hours in order to have access exclusively to all Study-related Documents relevant to the Budget and any pass through expenses paid by SPMSD under the present Agreement.

The provisions of this article shall survive expiration or otherwise termination of the present Agreement for whatever reason, and shall remain in full force and effect for an additional period of three (3) years after the ESR or first publication of the Study Results, whichever comes later.

9.3 Inspection by Health Authorities

The INSTITUTION shall further allow any Study inspections by local, European and/or international health authorities (hereinafter referred to as the "**Health Authorities**") in the INSTITUTION's premises/offices and shall keep SPMSD informed of such inspections. SPMSD should be informed of any major and critical findings dealing with activities falling under the scope of the present agreement.

If any Health Authorities conducts, or gives notice of its intent to conduct an inspection relating to the Study at the INSTITUTION premises, or takes any other regulatory action with respect to any Services performed under the present Agreement, the Party learning thereof shall promptly give the other Party notice thereof, and each Party shall provide the other Party with any information reasonably required in connection therewith, such as but without limitation major and critical findings.

disposizioni del presente Accordo ed in particolare dei Testi.

9.2 Audit Finanziari

Previa ragionevole preventiva comunicazione, SPMSD potrà effettuare controlli nei confronti dell'ISTITUZIONE presso i locali/uffici di quest'ultima durante l'orario lavorativo al fine di avere accesso esclusivamente a tutti i Documenti relativi allo Studio attinenti al Budget e a tutte le spese di trasferta pagate da SPMSD ai sensi del presente Accordo.

Le disposizioni del presente articolo avranno validità anche successivamente alla scadenza o cessazione per altra causa del presente Accordo, e rimarranno in vigore per un ulteriore periodo di tre (3) successivi all'ESR o alla prima pubblicazione dei Risultati dello Studio, a seconda di quale evento si verifichi successivamente.

9.3 Ispezioni da parte delle Autorità Sanitarie

L'ISTITUZIONE acconsentirà inoltre a qualsivoglia ispezione sullo Studio da parte delle autorità sanitarie locali, Europee e/o internazionali (di seguito le "**Autorità Sanitarie**") nei locali/uffici dell'ISTITUZIONE e terrà informata SPMSD in merito a tali ispezioni. SPMSD dovrà essere informata di ogni maggiore criticità emersa in riferimento alle attività rientranti nell'ambito del presente Accordo.

Nel caso in cui qualsivoglia Autorità Sanitaria conduca, o comunichi la propria intenzione di condurre una ispezione relativa allo Studio presso le strutture dell'ISTITUZIONE, o adotti qualsiasi altra azione di natura regolamentare con riguardo ai Servizi effettuati ai sensi del presente Accordo, la Parte che verrà a conoscenza di tale circostanza ne darà prontamente notizia all'altra Parte, e ciascuna Parte fornirà all'altra tutte le informazioni ragionevolmente richieste in connessione a ciò, come, ma non limitatamente, alle maggiori criticità emerse.

ARTICLE 10 – RESPONSIBILITY

10.1 SPMSD shall bear full and entire responsibility for the proper conduct of the Study, in particularly with regards to liability laws and regulations. SPMSD is liable for any and all individuals involved in the Study as well as for its own negligence.

SPMSD subscribes an appropriate liability insurance coverage that covers both SPMSD liability and the liability of any individual who

ARTICOLO 10 – RESPONSABILITA'

10.1 SPMSD sarà interamente responsabile della corretta conduzione dello Studio, con particolare riferimento alle leggi e regolamenti in materia di responsabilità. SPMSD è responsabile per ciascun soggetto coinvolto nello Studio così come per la propria negligenza.

SPMSD sottoscrive una apposita polizza assicurativa a copertura sia della responsabilità di SPMSD e sia della responsabilità di qualunque

may intervene in the Study on behalf of SPMSD. However and as provided far below, SPMSD liability insurance does not cover the INSTITUTION for any negligence, recklessness, intentional misconduct, omission or breach by the INSTITUTION of any of the guaranties and obligations in the course of the Study.

soggetto che dovesse intervenire nello Studio per conto di SPMSD. Tuttavia, come disposto di seguito, la polizza assicurativa per responsabilità di SPMSD non copre l'ISTITUZIONE per negligenza, imprudenza, cattiva condotta intenzionale, omissione o violazione da parte dell'ISTITUZIONE delle garanzie e degli obblighi nel corso dello Studio.

10.2 The INSTITUTION shall be responsible for, and will indemnify, defend and hold SPMSD, its Parent and Subsidiary Companies including SPMSD Local Contact (hereinafter collectively the "**SPMSD Indemnities**") harmless from and against all direct losses, costs, expenses, liabilities, actions, suits and damages of every kind and nature, including without limitation interest, penalties, reasonable attorney's fees and arbitration and/or litigation costs, based on or arising out of third party claims, including claims made by the Scientific Coordinator, brought against SPMSD as a result of any negligence, recklessness, intentional misconduct, omission or breach by the INSTITUTION of any of the warranties and obligations conferred to this latter by the present Agreement.

10.2 L'ISTITUZIONE sarà responsabile e terrà SPMSD e le Società Controllanti e Controllate di SPMSD, incluso il Contatto Locale (di seguito congiuntamente i "**Soggetti Risarciti di SPMSD**") indenni e manlevati da perdite dirette, costi, spese, responsabilità, azioni, procedimenti legali e danni di qualsiasi natura, ivi compresi, senza limiti, interessi, penali, competenze, spese legali e/o di arbitrato, derivanti o in qualche modo connessi a pretese/azioni legali di terzi, incluse le azioni del Coordinatore Scientifico, promosse nei confronti di SPMSD per negligenza, imprudenza, cattiva condotta intenzionale, omissione o violazione da parte dell'ISTITUZIONE delle garanzie e degli obblighi ad essa attribuiti nell'ambito del presente Accordo.

The INSTITUTION shall notify SPMSD immediately upon learning of any possible claims or similar events of any third party that may be brought against SPMSD and shall fully coordinate with SPMSD for any necessary actions.

L'ISTITUZIONE dovrà informare SPMSD immediatamente dopo essere venuta a conoscenza di ogni eventuale pretesa o evento similare da parte di terzi che potrebbe essere promossa nei confronti di SPMSD e dovrà coordinarsi con la stessa per ogni necessaria azione.

10.3 SPMSD shall be responsible for, and will indemnify, defend and hold the INSTITUTION (hereinafter the "**INSTITUTION Indemnities**") harmless from and against all direct losses, costs, expenses, liabilities, actions, suits and damages of every kind and nature, including without limitation interest, penalties, reasonable attorney's fees and arbitration and/or litigation costs, based on or arising out of third party claims brought against the INSTITUTION as a result of any negligence, recklessness, intentional misconduct, omission or breach by SPMSD of any of the warranties and obligations conferred to this latter by the present Agreement.

10.3 SPMSD sarà responsabile e terrà l'ISTITUZIONE (di seguito "**Soggetto Risarcito dell'ISTITUZIONE**") indenne e manlevata da perdite dirette, costi, spese, responsabilità, azioni, procedimenti legali e danni di qualsiasi natura, compresi, senza limiti, interessi, penali, competenze, spese legali e/o di arbitrato, derivanti o in qualche modo connessi a pretese/azioni legali di terzi promosse nei confronti dell'ISTITUZIONE per negligenza, imprudenza, cattiva condotta intenzionale, omissione o violazione da parte di SPMSD delle garanzie e degli obblighi ad essa attribuiti nell'ambito del presente Accordo.

SPMSD shall notify the INSTITUTION immediately upon learning of any possible claims or similar events of any third party that may be brought against the INSTITUTION and shall fully coordinate with the INSTITUTION or any necessary actions.

SPMSD dovrà informare l'ISTITUZIONE immediatamente dopo essere venuta a conoscenza di ogni eventuale pretesa o evento similare da parte di terzi che potrebbe essere promossa nei confronti dell'ISTITUZIONE e dovrà coordinarsi con la stessa per ogni necessaria azione.

10.4 Each Party shall indemnify and hold the other Party harmless from and against any and all

10.4 Ciascuna Parte dovrà tenere indenne e manlevare l'altra Parte da ogni azione o danno subito da

actions or damages suffered by the latter arising out of any failure to ensure compliance with the provisions of this Article.

10.5 Neither Party nor a Party's Indemnitees shall be liable for any special, incidental, indirect or consequential damages, including, but not limited to the loss of goodwill, loss of opportunity, loss of use, or loss of revenue or profit, in connection with or arising out of the present Agreement or the Services contemplated hereunder, even if such damages may have been foreseeable to such Party.

ARTICLE 11 – ENTRY INTO FORCE – TERM

11.1 The present Agreement shall enter into full force and effect on the last date of signatures written by the Parties below (the "**Effective Date** ") and shall remain valid until validation of the final Epidemiological Study Report which is expected by 31 December 2014. It may be extended or renewed on written and express agreement between the Parties. Publication rules shall remain valid for 5 years.

11.2 Notwithstanding the foregoing, this Agreement may be terminated at any time by written notice with acknowledgement of receipt in the following cases and conditions:

(a) by any Party if the other Party fails to observe, perform, or otherwise breaches any of its obligations under the present Agreement in any material respect in whole or in part, provided such failure continues for a period of two (2) weeks after receipt by the defaulting Party of written notice thereof from the other Party specifying such failure to rectify the same; or

(b) by SPMSD, within thirty (30) calendar days following receipt by the INSTITUTION of a written notice with acknowledgement of receipt for any other reason.

11.3 Any and all provisions, promises and warranties contained herein which by their nature or effect are required or intended to be observed, kept or performed after termination or expiration of this Agreement will survive the termination or expiration of this Agreement, as the case may be, and remain binding upon and for the benefit of the Parties thereto.

quest'ultima derivante da qualsivoglia inosservanza alle disposizioni del presente Articolo.

10.5 Nessuna Parte e nessun Soggetto Risarcito sarà responsabile per danni speciali, incidentali, indiretti o conseguenti, ivi comprese, ma non limitatamente ad esse, la perdita di avviamento, la perdita di opportunità, la perdita di uso, o la perdita di entrate o profitti, relativi al o derivanti dal presente Accordo o dai Servizi ivi contemplati, anche se tali danni avrebbero potuto essere previsti dalla Parte stessa.

ARTICOLO 11 – ENTRATA IN VIGORE - DURATA

11.1 Il presente Accordo decorrerà dall'ultima data di sottoscrizione delle Parti (di seguito la "**Data Effettiva**") e rimarrà in vigore sino alla validazione della Relazione dello Studio Epidemiologico finale, prevista per il 31 dicembre 2014. Potrà ssere prorogato o rinnovato con il consenso espresso per iscritto tra le Parti. Le regole di pubblicazione rimarranno in vigore per 5 anni.

11.2 Nonostante quanto sopra previsto, il presente Accordo potrà essere risolto in ogni momento previa notifica scritta con avviso di ricevimento, nei seguenti casi ed alle seguenti condizioni:

(a) da ciascuna Parte se l'altra manca di osservare, adempiere, o comunque viene meno ai propri obblighi derivanti dal presente Accordo in tutto o in parte, purché tali inadempimenti si protraggono per due (2) settimane dal ricevimento da parte della Parte inadempiente di un avviso scritto inviato dalla Parte non inadempiente che specifichi tale inadempimento al fine di porvi rimedio; o

(b) da SPMSD, entro 30 (trenta) giorni di calendario dal ricevimento da parte dell'ISTITUZIONE di una notifica scritta con ricevuta di ritorno per ogni ulteriore ragione.

11.3 Tutte e ciascuna delle disposizioni, impegni e garanzie contenuti nel presente Accordo che per loro natura o efficacia devono essere rispettati, osservati o eseguiti dopo la risoluzione o la scadenza del presente Accordo sopravvivranno a tale scioglimento o scadenza, a seconda del caso, e resteranno vincolanti tra ed a beneficio delle Parti.

11.4 The Parties shall meet to settle the amounts owed to the INSTITUTION at the termination date of this Agreement, it being understood that all work performed by the INSTITUTION for the Services hereunder at the termination date shall be paid by SPMSD pursuant to article 6 above.

11.4 Le Parti si incontreranno per definire gli importi dovuti all'ISTITUZIONE alla data di scadenza del presente Accordo, restando inteso che tutto il lavoro eseguito dall'ISTITUZIONE per i Servizi resi nell'ambito del presente Accordo dovranno essere corrisposti da SPMSD in virtù del precedente articolo 6.

ARTICLE 12 – REPRESENTATION - WARRANTIES– LABOUR AND TAXES OBLIGATIONS

ARTICOLO 12 – DICHIARAZIONI – GARANZIE - OBBLIGAZIONI FISCALI E PREVIDENZIALI

12.1 The INSTITUTION represents and warrants to SPMSD that the INSTITUTION has the right to enter into this Agreement, namely vis-à-vis any other person or entity with which it may have contractual relationships and/or vis-à-vis any other administrative authority, and to be bound by its provisions.

12.1 L'ISTITUZIONE dichiara e garantisce a SPMSD che l'ISTITUZIONE ha i necessari poteri per sottoscrivere il presente Accordo, in particolare nei confronti di ogni altra persona o entità con la quale può intrattenere rapporti contrattuali, e/o di ogni altra autorità amministrativa, e di essere vincolata alle prescrizioni in esso contenute.

12.2 The INSTITUTION represents and warrants to SPMSD that the INSTITUTION and the Scientific Coordinator have respectively the qualifications and abilities to perform the Services in a professional manner, without the advice, control and supervision of SPMSD.

12.2 L'ISTITUZIONE dichiara e garantisce a SPMSD che l'ISTITUZIONE ed il Coordinatore Scientifico hanno rispettivamente le qualifiche e le capacità necessarie per eseguire i Servizi in modo professionale, senza la consulenza, il controllo e la supervisione di SPMSD.

12.3 In accordance with French laws and regulations against dissimulated work and illegal employment (article L.8222-1 and D.8222-5 of the French Labour Code) SPMSD shall secure the INSTITUTION's situation with regards to labour laws and regulations.

Consequently the INSTITUTION warrants to SPMSD that the Services governed by the present Agreement are performed by employees (including the Key Personnel) who are lawfully employed in accordance with any and all labour laws and regulations applicable to the present Agreement.

12.3 In conformità con le leggi ed i regolamenti di diritto francese contro il lavoro nero e l'impiego illegale (articoli L.8222-1 e D.8222-5 del Codice del Lavoro Francese) SPMSD dovrà assicurare la situazione dell'ISTITUZIONE con riferimento alla normativa giuslavoristica.

Conseguentemente, l'ISTITUZIONE garantisce a SPMSD che i Servizi oggetto del presente Accordo vengono eseguiti da dipendenti (compreso il Personale Qualificato) impiegati legalmente nel rispetto della normativa in materia giuslavoristica applicabile al presente Accordo.

ARTICLE 13 - MISCELLANEOUS

ARTICOLO 13 – VARIE ED EVENTUALI

13.1 **Software Property and User rights – Computerized transmission of data**

The software needed for the performance of the Services and developed by the INSTITUTION is and shall remain the exclusive property of the INSTITUTION. SPMSD acknowledges that no user rights for the aforementioned software are transferred to SPMSD by the INSTITUTION by virtue of the present Agreement.

Additionally, during data transmission from the INSTITUTION to SPMSD requiring the use of computer hardware/software to receive or read

13.1 **Proprietà del software e diritti dell'utilizzatore – Trasmissione elettronica dei dati**

Il software necessario per l'esecuzione dei Servizi sviluppato dall'ISTITUZIONE è e rimarrà di proprietà esclusiva dell'ISTITUZIONE. SPMSD riconosce che nessun diritto d'uso riguardante il predetto software è stato trasferito a SPMSD da parte dell'ISTITUZIONE in virtù del presente Accordo.

Inoltre, durante la trasmissione dei dati dall'ISTITUZIONE a SPMSD per la quale è necessario un hardware/software per la ricezione o

such data, the INSTITUTION agrees to make all commercially reasonable arrangements to protect SPMSD against the passing of any "virus" (either any computer program containing harmful functions to operations or the use of a computer that the said virus has infiltrated, or harmful to the data drive contained in the said computer) during or subsequent to the data downloading as a result of the data downloading.

lettura di tali dati, l'ISTITUZIONE si obbliga a stipulare ogni ragionevole accordo commerciale al fine di proteggere SPMSD dal passagio di "virus" (programmi per computer contenti funzioni dannose per le operazioni o l'utilizzo di computer dove sono infiltrati virus ovvero che sono nocivi per il driver dei dati contenuto nel computer) durante o successivamente al download (importazione) di dati causato da tale download di dati.

13.2 Entire Agreement

The present Agreement including its amendment(s) or annexes contains the entire understanding between the Parties.

Unless the Parties have expressly agreed otherwise, this Agreement shall apply to and supersede any other written or oral agreement between the Parties relating to the same subject matter as this Agreement, whether such other agreement was entered into before or after the effective date of this Agreement except the feasibility Study agreement which has the same value of the present Agreement and which is attached as Annex 3 of the present Agreement as a part hereof.

Agreements or stipulations in any amendment(s) or annexes that are contrary to any term of this Agreement shall be void, unless the Parties have expressly agreed in writing that such agreement or stipulation shall supersede the terms of this Agreement.

13.2 Intero Accordo

Il presente Accordo comprensivo dei relativi emendamenti o allegati costituisce l'unico ed il solo accordo tra le parti.

Salvo diverso espresso accordo tra le Parti, il presente Accordo annulla e sostituisce ogni altro accordo scritto o verbale avente un oggetto uguale al presente Accordo, sia che tale diverso accordo sia stato stipulato antecedentemente o successivamente la Data Effettiva del presente Accordo, salvo l'accordo sullo Studio di fattibilità avente un valore uguale al presente Accordo e che viene allegato a quest'ultimo (allegato 3) quale sua parte integrante.

Accordi o emendamenti o allegati che risultino contrari rispetto ai termini del presente Accordo saranno considerati nulli, salvo che le Parti abbiano espressamente concordato per iscritto che gli stessi valgano a sostituire i termini del presente Accordo.

13.3 Independence of the Parties

Nothing in the present Agreement shall be construed as creating a partnership, contract of employment or relationship of agency or principal between the INSTITUTION and SPMSD and the INSTITUTION does not represent that any such relationship exists. Neither shall employees of one Party be considered as employees of the other Party. Further neither Party has any authority to bind or act on behalf of the other Party without its express written consent.

13.3 Indipendenza tra le Parti

Nulla di quanto previsto nel presente Accordo potrà essere interpretato nel senso di creare una associazione, un contratto di lavoro, un rapporto di agenzia tra l'ISTITUZIONE e SPMSD, e l'ISTITUZIONE non dichiara che una tale relazione esiste. Allo stesso modo nemmeno i dipendenti di ciascuna delle Parti possono essere considerati dipendenti dell'altra Parte. Inoltre, nessuna delle Parti ha alcun potere di vincolare o di agire per conto dell'altra Parte senza il suo consenso espresso per iscritto.

13.4 Waiver

No failure, delay, relaxation or indulgence by any Party in exercising any right conferred on such Party by this Agreement shall operate as a waiver of such right, nor shall any single or partial exercise of any such right nor any single failure to do so, preclude any other or future exercise of it, or the exercise of any other right under this Agreement.

13.4 Rinuncia

Nessun ritardo, indulgenza o mancato esercizio di qualsiasi diritto attribuito dal presente Accordo a ciascuna Parte potrà essere considerato quale rinuncia a tale diritto, né l'esercizio parziale o l'esercizio di uno solo dei diritti ad essa attribuiti - o il suo mancato esercizio -potranno precludere l'esercizio futuro di tali diritti ovvero l'esercizio di ogni altro diritto contenuto nel presente Accordo.

13.5 Assignment and Delegation

13.5.1 THE INSTITUTION shall not assign any of its rights under this Agreement, except with the prior written consent of SPMSD. In any event SPMSD shall not unreasonably withhold its consent. Notwithstanding the foregoing all assignments of rights are prohibited under this section whether they are voluntarily or involuntarily, by merger, consolidation, dissolution, sale of stock, and change of control, operation of law or any other manner, except where such assignment of any rights hereunder is made to an affiliate entity.

13.5.2 The INSTITUTION shall not delegate any performance under this Agreement, except to an affiliate entity or with the prior written consent of SPMSD as set forth in article 4.5 above.

13.5.3 Any attempt by either Party to make an assignment of rights or delegation of performance in violation of this Agreement is a material default under this Agreement. Any purported assignment of rights or delegation of performance in violation of this section is null and void.

13.6 Amendment

None of the Parties shall be bound by any conditions, definitions, warranties, understandings or representations with respect to the present Agreement other than that as provided herein or as fully agreed in written with an amendment duly signed by the representative of the Parties.

13.7 Severability

In the event any provision of this Agreement is inconsistent with or contrary to any applicable law, rule, or regulation, the validity, legality and enforceability of the remaining provisions shall not be affected or impaired. The Parties shall discuss in good faith the replacement of such inconsistent or contradictory provision with a valid, legal and enforceable provision with respect to the spirit of the Agreement and the Parties' common understanding.

13.8 Use of the name and logo

The Parties commit themselves not to use the corporate name and/or corporate logo of the other Party, neither the name of a member of the other Party's staff, nor the name of a representative of the other Party in any announcement, oral presentation or publication

13.5 Cessione e Delega

13.5.1 L'ISTITUZIONE non potrà cedere alcuno dei propri diritti derivanti dal presente Accordo, salvo che con il previo consenso scritto di SPMSD. SPMSD non potrà negare irragionevolmente il proprio consenso. Nonostante quanto sopra, qualsiasi cessione dei diritti è vietata ai sensi del presente articolo, sia volontaria che involontaria, mediante fusione, consolidamento, scioglimento, cessione di azioni, cambio di controllo, operazioni di legge o in qualsiasi altro modo, salvo il caso in cui la cessione dei diritti di cui al presente Accordo venga effettuata ad una società controllata.

13.5.2 L'ISTITUZIONE non potrà delegare l'esecuzione di alcuna prestazione oggetto del presente Accordo, salvo che ad una società controllata o salvo il previo consenso scritto di SPMSD come prescritto nel precedente Articolo 4.5.

13.5.3 Ogni tentativo di cedere i propri diritti o di delegare l'esecuzione delle prestazioni oggetto del presente Accordo in violazione dello stesso è considerato un inadempimento materiale del presente Accordo. Ogni pretesa cessione dei propri diritti o delega dell'esecuzione del presente Accordo in violazione del presente articolo è nulla ed inefficace.

13.6 Emendamenti

Nessuna delle Parti sarà vincolata da qualsivoglia condizione, definizione, garanzia, intesa o dichiarazione relativa al presente Accordo diversa da quelle contenute nel presente Accordo, salvo che non sia stata successivamente concordata per iscritto mediante un emendamento debitamente sottoscritto dai rappresentanti delle Parti.

13.7 Divisibilità

Qualora una o più disposizioni del presente Accordo siano considerate illegali, invalide, contraddittorie o inapplicabili, tale illegalità, invalidità, contraddittorietà o inapplicabilità non riguarderà le altre disposizioni del presente Accordo. La Parti discuteranno in buona fede la sostituzione di tale clausola invalida o contraddittoria con una valida, legale ed applicabile nel rispetto dello spirito del presente Accordo e delle comuni intenzioni delle Parti.

13.8 Uso della ragione sociale e del logo

Le Parti si impegnano a non usare la ragione sociale e/o il logo della società dell'altra Parte, né il nome di un membro dello staff o di un rappresentante dell'altra Parte in alcun annuncio, presentazione orale, o pubblicazione riguardante lo Studio o in alcuna pubblicazione o materiale

relating to the Study or in any publication or promotional materials or other form for public distribution, without such Party's prior and written agreement.

promozionale o altra forma di distribuzione al pubblico, senza il preventivo accordo scritto di tale Parte.

ARTICLE 14- LITIGATION/ GOVERNING LAW / JURISDICTION

ARTICOLO 14 – CONTENZIOSO / NORMATIVA APPLICABILE / GIURISDIZIONE

14.1 In the event of a breach or threatened breach of any of the provisions of the present Agreement by the INSTITUTION, SPMSD shall have no adequate remedy at law and shall therefore be entitled to enforce any such provision by temporary or permanent injunction or mandatory relief obtained in any court of competent jurisdiction without the necessity of proving damages, posting any bond or other security and without prejudice to any rights and remedies which may be available at law or in equity.

14.1 Nell'ipotesi di inadempimento o minaccia di inadempimento delle clausole del presente Accordo da parte dell'ISTITUZIONE, SPMSD non avrà alcun adeguato rimedio di legge ed avrà pertanto il diritto di far rispettare tali clausole mediante ingiunzione o ordinanza del Tribunale competente, senza la necessità di fornire la prova dei danni, prestare cauzione o altre garanzie e senza pregiudizio per diritti e rimedi forniti dalla legge o secondo equità.

14.2 This Agreement shall be governed and construed in accordance with the laws of Italy.

14.2 Il presente Accordo deve essere disciplinato ed interpretato in conformità alla normativa italiana.

14.3 Any dispute or difficulty or misunderstanding over the interpretation or the enforcement of the present Agreement which the Parties cannot settle amicably within a period of sixty (60) days shall be finally settled by the competent courts of Florence (Italy).

14.3 Ogni controversia, difficoltà o malinteso in ordine all'interpretazione o applicazione del presente Accordo che le Parti non riusciranno a comporre amichevolmente entro il termine di sessanta (60) giorni, sarà di competenza esclusiva del Tribunale di Firenze (Italia).

14.4 Except as required by law, the controlling language of this Agreement is Italian and any dispute brought under this Agreement shall be conducted in Italian.

14.4 Salvo quanto richiesto dalla legge, la lingua ufficiale del presente Accordo è l'italiano e qualsiasi controversia promossa nell'ambito del presente Accordo dovrà essere condotta in italiano.

14.5 The Parties agree that this Agreement is written in both Italian and English languages for sake of clarity and that the English version is conforming to the Italian version. Notwithstanding the foregoing, the Parties agree in good faith that the Italian version shall in any case prevail on the English version which has no contractual value.

14.5 Le Parti concordano che il presente Accordo è redatto sia in italiano che in inglese per ragioni di chiarezza e che la versione inglese è conforme alla versione italiana. Nonostante quanto sopra, le Parti concordano in buona fede che la versione italiana sarà in ogni caso prevalente rispetto a quella inglese che non ha alcun valore contrattuale.

ARTICLE 15 – COUNTERPARTS

This Agreement is executed in three (3) counterparts each of which shall be deemed an original, but all together shall constitute one and the same instrument. This Agreement shall not be binding until each Party receives a signed original from the other Parties.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be duly executed as of the Effective Date.

Made in Lyon, France on behalf of:

Sanofi Pasteur MSD S.N.C.

Date:
Signature:

Dr Jean-Paul KRESS
President

The INSTITUTION

Date:
Signature:

Dr Gianni Amunni
General Manager

In the presence of:
Dr. Francesca Carozzi
The Scientific Coordinator

Date:
Signature:

ARTICOLO 15 – COPIE

Il presente Accordo viene eseguito in tre (3) esemplari ciascuno dei quali è considerato un originale, ma tutti insieme formano un unico e medesimo strumento. L'Accordo non sarà vincolante fino a quando ciascuna Parte non riceverà un originale sottoscritto dalle altre Parti.

IN CONSIDERAZIONE DI TUTTO QUANTO SOPRA DISPOSTO, le Parti hanno stabilito che il presente Accordo venga puntualmente eseguito a far data dalla Data Effettiva.

Lione, Francia, in nome e per conto di:

Sanofi Pasteur MSD S.N.C.

Data:
Firma:

Dr. Jean-Paul KRESS
Presidente

L'ISTITUZIONE

Data:
Firma:

Dr. Gianni Amunni
Direttore Generale

Alla presenza di:
Dr. Francesca Carozzi
Il Coordinatore Scientifico

Data:
Firma:

ANNEX 1

PROTOCOL
Final version dated 24 Jun 2011

ALLEGATO 1

PROTOCOLLO
Final version dated 24 Jun 2011

ANNEX 2
Financial provisions and List of services

Payment modalities

Payments by the Sponsor to the INSTITUTION shall be made as follows:

1. A first payment of 25 % of the total amount shall be made upon signature of this Agreement
2. a second payment of 20% of the total amount shall be made after half of HPV analyses
3. a third payment of 25% of the total amount shall be made after all HPV analyses
4. a fourth payment of 15% shall be made after the SPONSOR validation of the final statistical report
5. a final payment of 15 % shall be made after the Sponsor validation of the final ESR

Payment terms

Prior to each payment, the INSTITUTION shall establish an invoice as follows (mandatory elements except if mention of "if applicable"):

- Samantha ATRUX-TALLAU - Epidemiological Project Coordinator
- Sanofi Pasteur MSD S.N.C, Epidemiological Department Europe, 8 rue Jonas Salk, 69367 LYON Cedex 07 (France),
- Sanofi Pasteur MSD S.N.C. intra-European VAT number : FR04 392 032 934
- Name and address of the INSTITUTION ,
- the INSTITUTION's intra-European VAT number (if applicable)
- Study number: GDS02E
- Reference to payment schedule (first payment, second payment, etc.)
- The amount owed excluding VAT
- VAT amount
- The amount owed including VAT
- Banking information of the INSTITUTION issuing the invoice for bank transfer –

Each invoice shall be established as indicated above and shall be sent to the contact name at the address above mentioned.

List of services/activities to be sent by the INSTITUTION (including the Central Laboratory services) see budget grid (Excel file version N°01 dated 14Dec2011).

ALLEGATO 2
Disposizioni finanziarie ed Elenco dei servizi

Modalità di pagamento

I pagamenti dal Promotore all'ISTITUZIONE dovranno avvenire come segue:

1. Un primo pagamento pari al 25% dell'ammontare complessivo dovrà essere effettuato alla sottoscrizione del presente Accordo.
2. Un secondo pagamento pari al 20% dell'ammontare complessivo dovrà essere effettuato dopo la metà delle analisi HPV.
3. Un terzo pagamento pari al 25% dell'ammontare complessivo dovrà essere effettuato al termine delle analisi HPV.
4. Un quarto pagamento pari al 15% dovrà essere fatto a seguito della validazione da parte del Promotore del report statistico finale.
5. Il pagamento finale del restante 15% dovrà essere fatto a seguito della validazione da parte del Promotore dell'ESR finale.

Termini di pagamento

Prima di ogni pagamento, l'ISTITUZIONE dovrà emettere una fattura secondo le seguenti modalità (elementi obbligatori, salvo menzione "se applicabile"):

- Samantha ATRUX-TALLAU - Epidemiological Project Coordinator
- Sanofi Pasteur MSD S.N.C., Epidemiological Department Europe, 8 Rue Jonas Salk, 69367 LIONE Cedex 07 (Francia)
- Sanofi Pasteur MSD S.N.C. numero di partita IVA intra-comunitario: FR04 392 032 934
- Nome ed indirizzo dell'ISTITUZIONE
- Numero di partita IVA intra-comunitario dell'ISTITUZIONE (se applicabile)
- Numero dello Studio: GDS02E
- Riferimento alla tempistica di pagamento (primo pagamento, secondo pagamento, ecc.)
- Ammontare dovuto, IVA esclusa
- Ammontare dell'IVA
- Ammontare dovuto, IVA inclusa
- Coordinate bancarie dell'ISTITUZIONE che emette la fattura per il bonifico bancario.

Ogni fattura dovrà essere emessa come sopra indicato e dovrà essere inviata all'attenzione del referente all'indirizzo suindicato.

Elenco dei servizi/attività da inviare a cura dell'ISTITUZIONE (inclusi i servizi del Laboratorio Centrale) vedi griglia di budget (Excel versione file n. 01 del 14Dic2011).

ANNEX 3

Copy of the feasibility Study agreement dated 30 December 2010

ALLEGATO 3

Copia dell'accordo sullo Studio di fattibilità del 30 dicembre 2010

PROTOCOL

Monitoring HPV Type Prevalence in the Post-vaccination Era in Women Living in the Basilicata Region, Italy

Sponsor	Sanofi Pasteur MSD SNC 8, rue Jonas Salk 69367 LYON CEDEX 07, France
Study Identification Number (SIN)	GDS02E
Sponsor's Study Manager / Signatory	Laurence Serradell, Epidemiological Project Manager Department of Epidemiology, Europe Sanofi Pasteur MSD SNC Tel.: +33 (0)4 37 28 43 88 Fax: +33 (0)4 37 28 44 51
Scientific Coordinator (SC)	Francesca Carozzi, Molecular biologist Istituto per lo Studio e la Prevenzione Oncologica (ISPO) Unità Operativa Citologia Analitica e Molecolare Villa delle Rose Via Cosimo il Vecchio, 2 50127 Firenze, Italy
Principal Investigator (PI) responsible for study enrollment and clinical procedures:	Pasquale Silvio Anastasio, MD, Gynaecologist Ospedale Madonna delle Grazie di Matera Unità Operativa di Ostetrica e Ginecologica Azienda sanitaria Locale di Matera A.S.M. Via C.da Ambulante 75100 Matera (MT), Italy
Principal Investigator (PI) responsible of vaccination center	Espedito Antonio Moliterni, MD, Hygienist Dipartimento di prevenzione Azienda sanitaria Locale di Matera ASM Via Montescaglioso, 20 75100 Matera (MT), Italy
Version	Final
Date	24 June 2011

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ABBREVIATIONS

AB	Advisory Board
AGC	Atypical Glandular Cells
ASC-US	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical Squamous Cells where HSIL cannot be excluded
CCTIRS	Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé/Advisory Board for information processing
CNIL	Commission Nationale de l'Informatique et des Libertés/French Data Protection Authority
CRO	Contract Research Organization
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Epidemiological Practice
GISCi	Gruppo Italiano Screening Cervicocarcinoma
HC2	Hybrid Capture 2
HPV	Human Papillomavirus
HR	High-risk
HSIL	High-grade Squamous Intra-epithelial Lesion
ICF	Informed Consent Form
ISPO	Istituto per lo Studio e la Prevenzione Oncologica
ISTAT	Istituto Nazionale di Statistica
LHU	Local Health Unit
LR	Low-risk
LSIL	Low-grade Squamous Intra-epithelial Lesion
Pap test	Papanicolaou test
PCR	Polymerase Chain Reaction
PF	Participant Form
QC	Quality Control
SC	Steering Committee
SPF	Short PCR Fragment
SPMSD	Sanofi Pasteur MSD
STM	Specimen Transport Medium
WMA	World Medical Association

1. GENERAL INFORMATION

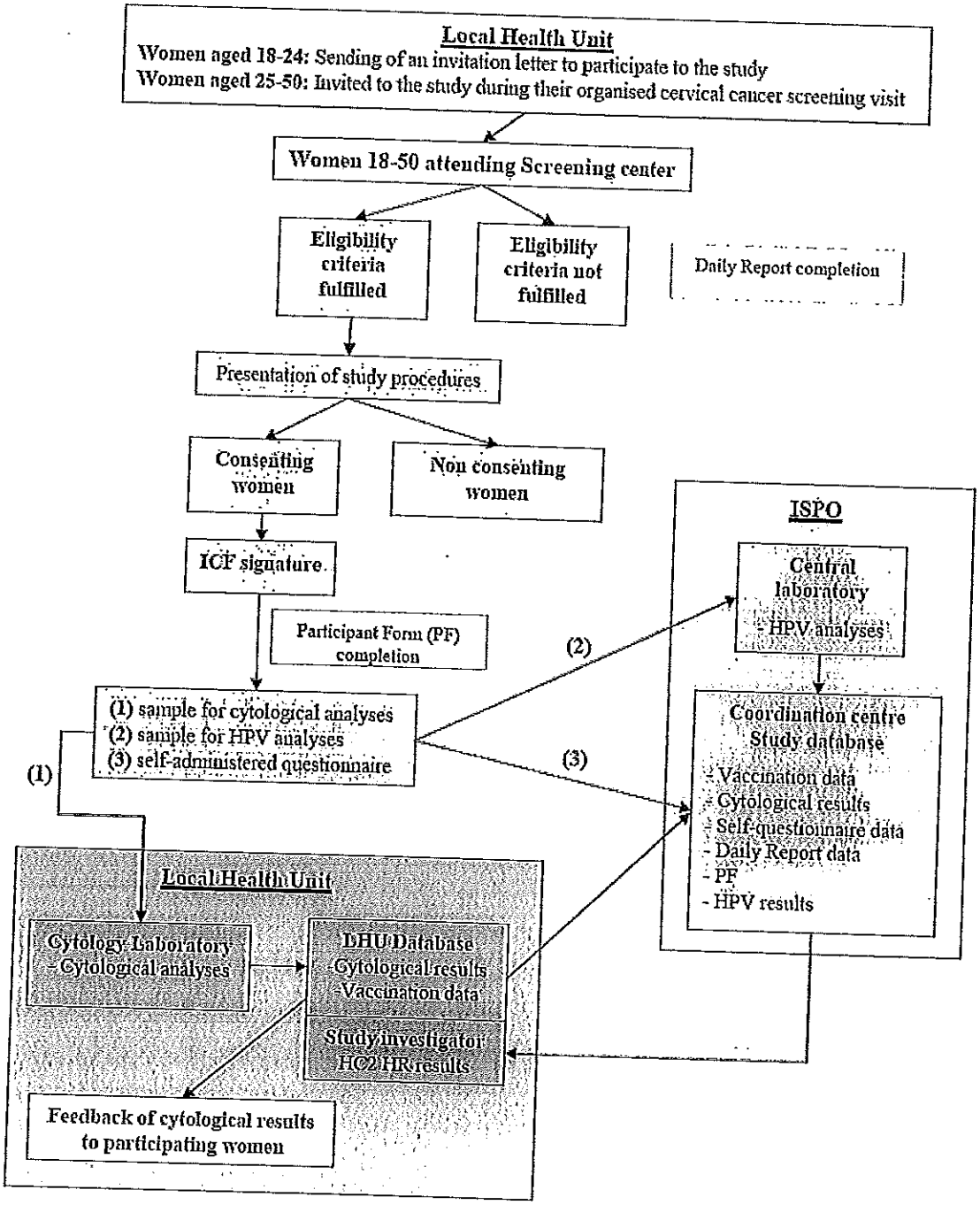
1.1 Contact list

SPMSD Europe	**Laurence Serradell, Epidemiological Project Manager** **Samantha Atrux-Tallau, Epidemiological Projects Coordinator** SPMSD Epidemiology Department, Europe 8, rue Jonas Salk, 69367 Lyon cedex 07 France
SPMSD Italy	**Emilia Perinetti, Clinical & Epidemiology Manager** SPMSD Scientific and Development Department Via degli Aldobrandeschi, 15 00163 Rome, Italy
Principal Investigator, responsible for study enrollment and clinical procedures:	Pasquale **Silvio Anastasio, MD, Gynaecologist** Ospedale Madonna delle Grazie di Matera Unità Operativa di Ostetrica e Ginecologica Azienda sanitaria Locale di Matera A.S.M. Via C.da Ambulante 75100 Matera (MT), Italy
Principal Investigator, responsible for vaccination centre:	**Espedito Antonio Moliterni, MD, Hygienist** Dipartimento di prevenzione Azienda sanitaria Locale di Matera ASM Via Montescaglioso, 20 75100 Matera (MT), Italy
Scientific Coordinator	**Francesca Carozzi, Molecular biologist** Istituto per lo Studio e la Prevenzione Oncologica (ISPO) Unità Operativa Citologia Analitica e Molecolare Villa delle Rose Via Cosimo il Vecchio, 2 50127 Firenze, Italy
Data Management and Statistics - ISPO	**Donella Puliti, Data Manager and Statistician** Istituto per lo Studio e la Prevenzione Oncologica (ISPO) Clinical and descriptive Epidemiology Unit Presidio di Ponte Nuovo Via Cosimo il Vecchio, 2 50127 Firenze, Italy
CRO	**Ulbricht Claudia, Project Manager** Omnicare Clinical Research operating as Theorem Clinical Research Via Luciano Manara, 1 23807 Merate (LC), Italy

1.2 Planned Study calendar

Action	Timelines
Regulatory documents preparation submission/approval	June 2010-Nov 2011
Participant recruitment	Nov 2011- April 2013
Laboratory analyses	Nov 2011- April 2013
Database management	Sept 2011- June 2013
Statistical analyses	July 2013–Sept 2013
Final study report	December 2013

1.3 Flow chart



1.4 Signature page

On behalf of Sanofi Pasteur MSD:

Signature: Laurence Serradell

Date:

On behalf of the Scientific Coordinator:

Signature: Francesca Carozzi

Date:

On behalf of the Principal Investigator for cervical screening:

Signature: Pasquale Silvio Anastasio

Date:

On behalf of the Principal Investigator for vaccination:

Signature: Espedito Antonio Moliterni

Date:

2. SYNOPSIS

Sponsor	Sanofi Pasteur MSD (SPMSD)
Title of the study	Monitoring HPV Type Prevalence in the Post-vaccination Era in Women Living in the Basilicata Region, Italy
Study Identification Number (SIN)	GDS02E
Vaccines or disease area	Gardasil®; Human Papillomavirus
Investigators	– Investigational centre: • Local Health Unit (LHU) of Matera in the Basilicata region (16 screening centres included in the study) – Principal Investigators: • Dr. Pasquale Silvio Anastasio (cervical screening; Matera's LHU) • Dr. Espedito Antonio Moliterni (vaccination; Matera's LHU)
Planned study period	**2011-2013** (Recruitment period: ~12-18 months)
Inclusion and Non-inclusion criteria	– Inclusion criteria: • Women between 18-24 years old invited to the study • Women between 25-50 years old invited within the frame of the organised cervical cancer screening program • Signing an Informed Consent Form (ICF) to participate in the study – Non-inclusion criteria: • Virginal women • Hysterectomized women • Women who underwent colposcopy in the 24 months prior the enrolment visit
Background and Rationale	Gardasil® is a quadrivalent vaccine against HPV types 6/11/16 and 18. Following the introduction of HPV vaccines, there is a theoretical concern that the niche created by the elimination of vaccine types will be taken over by other non-vaccine types. The major concern would be that non-vaccine oncogenic HPV types (HPV High-risk types) fill the niche vacated by vaccine types and result in a less than expected decrease in HPV-related diseases. This phenomenon will need to be monitored. A study which will generate information to assess potential type replacement is being conducted in four Nordic European countries (Denmark, Iceland, Norway and Sweden) by Merck (one of SPMSD Shareholders) following a request from the U.S. Food and Drug Administration (FDA). The European Medicines Agency (EMA) asked SPMSD "to investigate the HPV type specific prevalence and potential non-vaccine type replacement in the post-vaccine era in non-Nordic European countries" in 2006 in order

Sponsor	Sanofi Pasteur MSD (SPMSD)
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	to support Gardasil® licensure in Europe. In the Italian region of Basilicata, HPV vaccination (with Gardasil®) and cervical screening are well-organized and individual data from both programs are registered in computerized registries. Women between 25 and 64 years old are invited to perform a Pap test every 3 years within the frame of the organized cervical screening program. Women at ages 11, 14, 17 and 24 have been invited for free of charge HPV vaccination with Gardasil® since 2007. We propose to conduct a cross-sectional study to estimate the overall and type-specific prevalence of cervical HPV infection (overall and stratified by the HPV vaccination status) among women aged 18-50 years living in the Basilicata region (Italy) in 2011-2013.
Objectives	– Primary objective: • To assess the overall and age-stratified prevalence of: o cervical HPV infection o cervical infection with HR types, HR non-vaccine types, LR types, LR non-vaccine types, vaccine types and by HPV type – Secondary objectives: • To assess the overall and age-stratified prevalence by cytological results and/or vaccination status (if final study sample allows it) -of cervical HPV infection -of cervical infection with HR types, HR non-vaccine types, LR types, LR non-vaccine types, vaccine types and by HPV type -of single and multiple HPV infections • To assess the overall and age-stratified prevalence of normal and abnormal cytological smears for the entire population and stratified by vaccination status (if final study sample allows it) • To evaluate the relationship between cervical HPV infection and potential risk factors (including demographics data, lifestyle habits and medical history)
Study design	Cross-sectional population-based descriptive study conducted on 18-50 year-old women living in Basilicata, Italy, in 2011-2013. Population source is: – Women between 18 and 24 years old at the time of invitation, living in Basilicata. – Women between the ages of 25-50 at the time of invitation (25 and 50 included), invited to the organized cervical cancer screening in Basilicata.
Regulatory procedures	Women aged 18-24 will be invited to participate by letter in the study. Women aged 25-50 will be invited during their organized cervical cancer

Sponsor	Sanofi Pasteur MSD (SPMSD)
Title of the study	Monitoring HPV Type Prevalence in the Post-vaccination Era in Women living in the Basilicata Region, Italy
Study Identification Number (SIN)	GDS02E
Vaccines or disease area	Gardasil®; Human Papillomavirus
	screening visit. Women will be informed about the procedures and data handling. Women who agree to participate in the study will sign an ICF before any study procedures. The study and the related procedures will be approved by the Italian local Ethic Committee of the site(s) involved. Data will be protected according to the Italian privacy law regarding the protection of personal data, Legislative Decree n.196/03. Data will also be treated and processed in compliance with the European Directive 95/46/EC regarding the data protection.
Planned sample size	In order to assess the impact of Gardasil® in terms of type replacement in the primary targeted age group, the younger population of women already targeted by the organized vaccination program (18-28 year old women) will be oversampled and overrepresented in the study population. 2,000 samples between the ages 18-28 and 1,500 in the ages 29-50 are expected to be sufficient to estimate prevalence of vaccine and HR non-vaccine types (ranging from 3 to 25%) with good half-width of the 95% CI. Considering that 10% of the samples might not be analyzable due to insufficient material for HPV testing, poor quality of the samples or loss of samples due to transport or storage problems, 3,890 women in total should be recruited **(2,223 women aged 18-28 and 1,667 women aged 29-50).** The table below provides the Half-width of a 95% confidence interval for prevalence ranging between 3 and 25%.

Age groups	Sample size (N)	Prevalence of HPV (either vaccine or HR-non vaccine types in %)								Sample size+ 1 drop out/missing
		3	3.3	4.5	5	10	15	20	25	
18-28	2,000	0.7	0.8	0.9	1.0	1.3	1.6	1.8	1.9	2,223
29-50	1,500	0.9	0.9	1.0	1.1	1.5	1.8	2.0	2.2	1,667
18-50	3,500	0.6	0.6	0.7	0.7	1	1.2	1.3	1.5	3,890

Data collection	– Daily report data. Aggregated data on: Number of women invited to the cervical cancer screening program, women attending the cervical cancer program (for 25-50 years old group). Number of women eligible/ineligible to the study, women enrolled/not enrolled in the study (for both age groups). – Participant Form data Information on inclusion/non-inclusion criteria fulfilled, participant number, date of birth, date of ICF signature, samples and questionnaire collected and dates of collection – "Self-administered questionnaires" data Socio-demographics variables; risk factors for HPV infection/cervical diseases; HPV vaccination status – Cytological results (using Bethesda 2001) – HPV vaccination status

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- HPV testing results
- HPV genotyping results

Data regarding the attendance rate to the cervical cancer screening program in areas covered by the screening centres involved in the study collected by the LHU will also be gathered.

The main study steps are described below. Differences in study processes exist between women aged 18-24 invited to cervical screening centres for the purpose of the study and women aged 25-50 attending the organized cervical screening program in Basilicata.

- Invitation process
  - Women aged 18-24

A list of 18-24 year-old women living in Basilicata will be generated from municipality registries. All the women will be invited through a study invitation letter. A second invitation letter (reminder) will be sent to all women failing to contact their screening centre 60 days after the first letter. In case of recruitment necessities women who are still failing to respond to the second invitation letter will be contacted by a third letter or phone call if possible.

  - Women aged 25-50

Women will be invited to participate into the study during their cervical cancer screening visit.

- Visit
  - Completion of the daily report by midwife/qualified staff member

A daily report will be completed in each participating center. This report will help to assess the representativeness of the study population and to assess the study participation rate among eligible women.

  - Study presentation

At the screening center, the study will be presented to the women by a midwife/qualified staff member. Women who are eligible and agree to participate in the study will sign an ICF before any study procedures. The Participant Form will be completed by midwife/qualified staff member for each participating woman. Women will be recruited in a consecutive manner.

  - Cervical sampling

The sample taker will perform a conventional Pap test for all study participants. For 25-50 years old women, the PAP test is part of the routine cervical screening. This sample will be used for cytological reading performed at local level.

A second cervical sample (sample in STM- specimen transport medium)

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Vaccines or disease area	Gardasil®; Human Papillomavirus
	will be collected within the frame of the study and will be sent to the central lab (ISPO Florence) for HPV analyses. • Self-administered questionnaire completion by participants After their screening visit, women will complete a self-administered questionnaire. – HPV analyses HPV testing will be performed using the HR/LR HC2 test. Samples with RLU/CO ratios ≥1 will be classified as HPV Positive samples; those with RLU/CO <1.0 as HPV Negative samples. HPV positive and 10% of randomly selected HPV-negative samples will be then genotyped using the INNO-LiPA extra test. All the analyses will be performed at a central laboratory (ISPO). – Data linkage For each participating woman, data collected for the purpose of the study (HPV status data, questionnaire data, PF), HPV vaccination status and cytological results will be linked at individual level (details provided in the core protocol) through the participant number and date of birth.
Data analysis	1.Description of the study population: A first part will consist in describing the study population. Quantitative variables will be described by their mean, standard deviation, median, quartiles, minimum/maximum. Categorical variables will be described by their frequency and percentage. The following variables will be described: age, country of birth, number of years living in Italy for people not born in Italy, smoking status, age at first sexual intercourse, number of sexual partners, contraceptives use, history of pregnancy, marital status, history of sexually transmitted diseases, educational level, professional status, and vaccination status. The representativeness of the study population will be assessed based on socio-demographic data provided by the self-administered questionnaire, compared to Italian national census data provided by ISTAT for the general female population. Characteristics of ineligible women will be assessed based on the daily report data and reasons for non participation among eligible women will be described. The concordance between HPV vaccination status collected in the vaccination database and collected through the self-administered questionnaire will be assessed. 2. Analyses answering the primary and secondary study objectives. The crude, age-standardized and age-stratified prevalence and their 95% CI stratified by cytological results and/or by vaccination status will be assessed. The age standardization will be made by the direct method using the most recent Italian census data as a reference (ISTAT data). The association between cervical HPV infection (dependent variable) and potential risk factors (independent variables) will be the object of a

Sponsor	Sanofi Pasteur MSD (SPMSD)
Title of the study	Monitoring HPV Type Prevalence in the Post-vaccination Era in Women Living in the Basilicata Region, Italy
Study Identification Number (SIN)	GDS02E
Vaccines or disease area	Gardasil®; Human Papillomavirus
	multivariate analysis using a logistic regression. Potential risk factors will include: age, country of birth, current marital status, smoking status, lifetime number of sexual partners, number of sexual partners in the last 6 months, history of abnormal Pap test, history of previous genital warts, current status and history of having sexually transmitted infection and immuno-suppression status. A first step will be dedicated to study the association between HPV infection and each risk factor will be assessed in univariable analyses (simple logistic regression analyses). Then, risk factors for which a significant association ($p<0.10$) is found will be considered in the multivariable analysis (multiple logistic regression).
Report and publication	A report will be prepared summarizing the study results. The results will be presented at international conferences (abstract, poster, oral presentation) and published in peer-reviewed journals.

3. BACKGROUND

Vaccination with Gardasil® was introduced in Europe in September 2006. Gardasil® is a vaccine indicated for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), cervical cancer and external genital warts (condyloma accuminata) causally related to HPV types 6, 11, 16 and 18. The vaccine is currently recommended for young girls and women between 9 and 26 years of age. Following the introduction of Gardasil®, the European Medicines Agency (EMA) has requested Sanofi Pasteur MSD to assess the HPV type prevalence and potential non-vaccine HPV type replacement in the post-vaccine era in non-Nordic European countries. Sanofi Pasteur MSD has suggested conducting a study on women aged 18-50 in the Italian region of Basilicata.

3.1 Epidemiology of Human Papillomaviruses

Genital Human Papillomavirus (HPV) infection is the most common sexually transmitted viral infection worldwide with approximately 75% of sexually active persons exposed to HPV in their lives[1]. Genital HPV infection is related to various clinical conditions ranging from asymptomatic infections to benign and malignant diseases of the mucosa. HPVs cause warts and have been well-established as the sexually transmitted agents that cause most invasive cervical cancers and their pre-cancerous lesions. However, most infected individuals clear the virus without ever developing clinical symptoms in a rapid manner (most women infected with a specific HPV type will not show evidence of that same type 6-12 months later). Thus, very few infected individuals progress to invasive cervical cancer[2]. Among the 40 HPV types that can infect the genital tract, HPV types are distinguished between high-risk (HR) types and low-risk (LR) types according to their degree of risk for development of cervical cancer. Infection with HR HPV is found in virtually all cases of cervical cancer and is considered as a necessary cause of invasive cervical cancer [2].

HPV 16 and 18 are responsible for approximately 70% of cervical cancers worldwide (54% and 16% for HPV 16 and 18, respectively). The remainder of cancers is linked to other oncogenic HPV types mainly HPV types 45 and 31 (responsible for 10% of cervical cancers) and then HPV 33 and 52 that contribute approximately another 5-7% [3].

Acquisition of HPV is particularly common among sexually active young adults and decreases with increasing age. Risk factors for HPV infection are: number of lifetime sexual partners, age at first sexual intercourse. Some studies found a positive association between HPV infection and smoking status (current/past smoking)[1]. Regarding the risk of cervical cancer, a linear positive dose-response relationship with duration of oral contraceptive use has been shown[4]. Active/passive smoking and existence of other STI are also risk factors for persistent HPV infection or co-factors for the development of cervical cancer. Some endogen hormones (number of pregnancies, menopausal status), immune deficiency and some nutritional factors are also involved [1].

3.2 Type replacement

3.2.1 General considerations on type replacement [5]

Vaccination (and chemotherapy as well) can destabilize the existing host-pathogen evolutionary equilibria or accelerate pathogen evolution leading to the phenomenon of treatment-induced pathogen strain replacement.

Generally speaking, strain replacement is the substitution over time of one or more initially dominant strains of a pathogen by another strain or strains. It occurs through the interaction of dynamics at two levels:

- Within-host (individual level) strain replacement is the replacement of a strain that dominated the initial infection of a particular host by a new strain without any intervening recovery period.
- Between host (population-level) strain replacement occurs when a once-common strain in the population becomes rare, while a second (previously rare) strain increases to a prevalence

greater than that of the first strain due to a deterministic process (rather than, say, ecological drift in a rare host population).

By definition, strain replacement is a consequence of increased absolute fitness (at the population level) of the replacement strain, and/or decreased fitness of the initial strain. The deployment of a treatment such as vaccination changes conditions (e.g. the proportion of hosts susceptible to one or the other strain). This in turn changes the competitive balance between strains and hence their absolute fitnesses, ultimately shifting their relative and absolute abundance. In practice, researchers use widely varying criteria to infer strain replacement. The only common element is an observed decline in the prevalence of vaccine strains accompanied by an increased prevalence of at least one non-vaccine strain.

The currently accepted model as the cause of type replacement relies on the selective nature of vaccine protection. If two types of strains are considered: vaccine strains and strain(s) that suffer significant cross-immunity as strains 1 and strains that at least partially escape the vaccine as strains 2. Before vaccination introduction, it is assumed that prevalence of strains 1 is higher than prevalence of strains 2 (under the assumptions that are typically targeted dominant strains). After vaccination introduction, strains 2 can still infect vaccinated individuals and no longer have to compete with strains 1 and consequently type replacement can occur. Unvaccinated people are protected through herd immunity. Herd immunity against strains 1 further reduces competition between strains for susceptible individuals. By reducing the prevalence of the dominant strains (strains 1) a differentially effective vaccine frees available host resources allowing strains 2 to proliferate and driving population-level type replacement.

3.2.2 Type replacement and HPV

Following the introduction of HPV vaccination, there is a theoretical concern that eradication of some HPV types will cause post-vaccination emergence of diseases caused by types not included in the vaccine. Two conditions seem needed for a type replacement to occur: (1) the existence of partial competition of different types during natural infection and (2) the vaccine should not offer cross-protection against types naturally competed against.

Based on the literature, possible competition between infections with different HPV types does not seem to exist. The presence of type-specific antibodies for one HPV type is associated with a strongly increased risk for also being seropositive for other HPV types which is in the opposite tendency. In addition, there are no clear examples of types of HPV DNA that do not go together (which should be expected if competition does exist). The second pre-requisite, cross-protection, has also been suggested by clinical trials [6]. For these reasons, HPV type replacement is often considered unlikely.

The figure 1 (courtesy: Pr Dillner) shows the hypothetical impact of HPV vaccination with Gardasil® on CIN2/3 incidence. Two scenarii are represented:

- The existence of a **cross-protection**: protection against HPV 16 will also protect against HPV 31 leading to a parallel decrease in the incidence of CIN2/3 lesions due to type 31. This phenomenon could lead to a benefit of the vaccine higher than expected.
- The existence of a **type replacement**: increase in the incidence of CIN2/3 lesions due to type 31 due to the elimination (partial or total) of HPV type 16. This phenomenon could lead to a benefit of the vaccine less than expected.

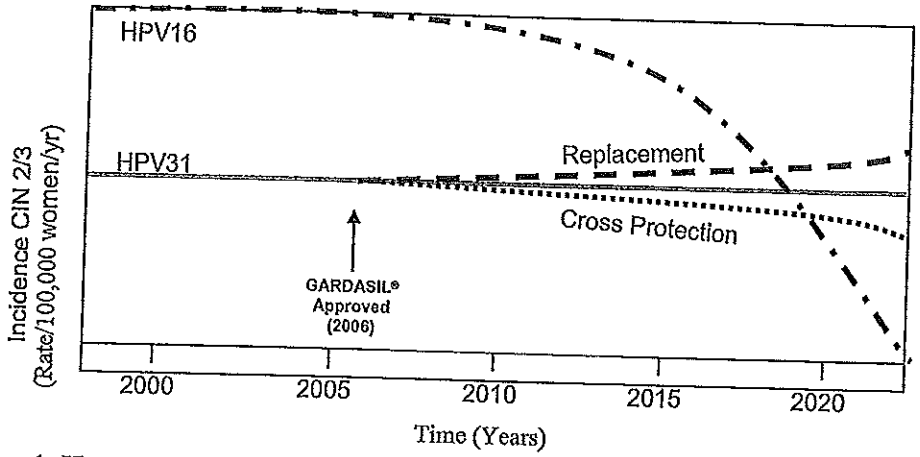

Figure 1: Hypothetical Changing Incidence of Vaccine Type and Non-Vaccine Type

The main concern with HPV-related diseases (and main difference between HPV-related diseases and the other vaccine preventable diseases) is the delay (many decades) between infection and the major diseases to be prevented by the vaccine. Consequently, this type of picture should only be seen in decades after HPV vaccine introduction.

Prevention of cervical cancer is the most expected clinical benefit of HPV vaccination. Trials have used surrogate end-points because cancers develop slowly and cancers as an end-point require unrealistic large and lengthy studies. Clinical management requires premalignant lesions to be treated immediately, making cancer both unfeasible and unethical as end-point in clinical trial setting. However, this concern could be also considered in surveillance studies as it should be unethical to wait appearance of cancers to detect a non-vaccine type replacement.

Protection against infection seems to be an obvious end-point for an infectious disease [6]. Proximal measures of vaccine impact include outcomes such as HPV infection, cervical cancer precursors, vaginal and vulvar cancer precursors and anogenital warts. Proximal measures are optimal for monitoring because they will detect an impact earlier than cancer outcomes [7]. Based on this, HPV type prevalence in the general female population should be considered primarily (with HPV types prevalence in cervical diseases secondly) to assess any changes following the introduction of HPV vaccination and assess a potential non-vaccine type replacement.

The 'type replacement' issue can be addressed only in large, statistically powerful long-term studies and post-vaccine surveillance will be critical in this regard [8].

3.2.3 How to study type replacement?

According to Martcheva et al.[5], both clinical trials and case-control studies are not well-adapted designs to assess a potential non-vaccine type replacement. The most appropriate studies for type replacement are surveillance studies. Most surveillance studies monitor increases in non-vaccine strains in the general population without regard to the individual's vaccine status but leave the causal link uncertain. Surveillances conducted to survey strain prevalence/type replacement are continuous surveillances (active or passive), for example based on networks of laboratories/hospital reports/national reference centres. Others are repeated cross-sectional studies over time [6].

3.3 Epidemiology of HPV infection and HPV-related diseases in Italy

In Italy, it is estimated that every year 3,418 women are diagnosed with cervical cancer and of those 1,186 die from the disease. Cervical cancer is the 10th most frequent cancer in Italy and the third

among women between 15 and 44 years. The incidence of cervical cancers is estimated at 11.6 per 100,000 women. 71.7% of invasive cervical cancers are attributable to HPV 16 or 18. HPV prevalence for the whole Italy in women with normal cytology has been estimated at 10.3% (IC95% [8.9-11.9]), 72.4% (IC95% [70.3-74.6]) in women with low-grade lesions, 85.6% (IC95% [78.2-91.2]) in women with high-grade lesions [9].

Several studies have been conducted in Italy both on women attending the cervical cancer screening (organized or not) and on younger women. Three of them are described below according to the age ranges targeted by this study protocol.

3.3.1 Women aged 18-24

A study conducted in Sicily in women between 18 and 24 years old (N= 1,006 women) in 2006-2007 shows that 24.1% (IC95% [21.5-26.9]), of the participating women were infected with HPV and 17.1% were infected with HR-HPV types. The most frequent type was HPV 16 with a prevalence of 4.5%, followed by HPV 53 identified in 2.7%, HPV 84 in 2.6%, HPV 42 in 2.5%, HPV 62 in 2.4% and HPV 66 as well as HPV 89 in 2.2%. The prevalence of vaccine types HPV 6, HPV 11 and HPV 18 was 1.4%, 0.1% and 1.3% respectively [10].

A more recent study conducted in Toscana areas in 2007-2008 in randomly selected 18-24 women (N= 1,066) shows that 19.32 % of women were infected by HPV HR and 10.03 % by HPV LR. Infections with HPV HR alone were detected in 13.7% of women, infection with HPV LR types alone in 4.41% and co-infections with both HPV HR and LR in 5.63% of women. HPV 16 was the most prevalent type (8.53%), followed by HPV 31 and HPV 56 (2.44%), HPV51 (2.06%) and HPV18 (1.88%). The HPV LR types 6 and 11 were detected in 3.47% and 4.12% of women respectively [11].

These two studies showed a high prevalence of genital HPV infections in young Italian women.

3.3.2 Women aged 25-70

An Italian cross-sectional study was conducted in 2002 in order to assess the prevalence of cervical HPV infection in women attending cervical cancer screening in Turin (this screening program invites women aged 25-64 every 3 years to perform a Pap test) (N=1,025 women). HPV DNA was detected using the GP5+/GP6+ PCR assay. The overall HPV prevalence was 8.8% in women aged 25-70 years. HPV prevalence was 13-14% at age 25-39 years, 11.5% at age 40-44 years and approximately 5% in the older age groups. The prevalence of HPV 6, 11, 16 and 18 was 0.1%, 0.2%, 2.9% and 0.1% respectively for all included women. However, Turin is an industrial city in North-western Italy and cannot be considered representative of Italy as a whole [12].

3.4 Italian public Health organization and programs

Italy's health care system is a regionally based national health service. The system is organized at three levels: national, regional and local. At the regional level, regional governments through the regional health departments are responsible for ensuring the delivery of a benefit package through a network of population-based health management organizations and public and private accredited hospitals. Cervical cancer screening and vaccination programs are managed by the Public Health system through LHUs.

3.4.1 Cervical cancer screening in Italy

In most of the Italian regions, organized cervical cancer screening programs exist. Within these programs, women aged 25-64 years are invited every 3 years to perform a Pap test. Individual data regarding the cytological results are registered in computerized registries.

3.4.2 HPV vaccination policy in Italy

The HPV vaccination was introduced in Italy in 2007.. In most of the Italian regions, young girls aged 11 years are invited for a free-of-charge vaccination. Women not involved in the active vaccination programs can be vaccinated until 26 years but are not or only partially reimbursed. Data from vaccinated women (name of the vaccine, dates of vaccination) are in most of the cases registered in computerized registries.

3.5 Rationale

3.5.1 EMA commitment

Gardasil® is a quadrivalent vaccine against HPV types 6/11/16 and 18. Following the introduction of HPV vaccines, there is a theoretical concern that the niche created by the elimination of vaccine types will be taken over by other non-vaccine types. The major concern would be that non-vaccine oncogenic HPV types (HPV high-risk types) fill the niche vacated by vaccine types and result in a less than expected decrease in HPV-related diseases. This phenomenon will need to be monitored.

A study which will generate information to assess potential type replacement is being conducted in four Nordic European countries (Denmark, Iceland, Norway and Sweden) by Merck (one of SPMSD shareholders) following a request from the U.S. Food and Drug Administration.

The European Medicines Agency (EMA) asked SPMSD "to investigate the HPV type specific prevalence and potential non-vaccine type replacement in the post-vaccine era in non-Nordic European countries" in 2006 in order to support Gardasil® licensure in Europe.

3.5.2 Rationale to conduct a study to determine the type-specific prevalence and a potential type replacement in the Italian region of Basilicata

The choice of Italy is mainly due to the organization and management of primary prevention in this country: presence of computerized vaccination and screening registries, type of data recorded and possibility of link registries. The region of Basilicata has been more precisely selected due to 2 main aspects:

1. An organized cervical screening program gathering individual data on cytological results in a computerized registry
2. An organized HPV vaccination program (has been) in place with Gardasil® (only vaccine available) since 2007. This vaccination is free-of-charge for women aged 11, 14, 17 and 24 years as in most of other Italian regions the vaccination is for 11-year-old girls. Catch-up programs are in place and girls invited at 11 years, who did not attend the program, are invited again at 14 years, then at 17 years if they did not attend (similar processes exist for girls aged 14 and 17 years). The unique vaccination program in place in this region offers the opportunity to gather data on vaccinated women (by considering women aged 18-50 in the study).

We suggest conducting a cross-sectional study to estimate the overall and type-specific prevalence of cervical HPV infection (overall and stratified by HPV vaccination status) among women aged 18-50 years living in the Basilicata region (Italy).

4. STUDY OBJECTIVES

- Primary objective:
  - To assess the overall and age-stratified prevalence
    -of cervical HPV infection
    -of cervical infection with HR types, HR non-vaccine types, LR types, LR non-vaccine types, vaccine types and by HPV type

- Secondary Objectives:
  - To assess the overall and age-stratified prevalence by cytological results and/or vaccination status (if sample size allows it)
    -of cervical HPV infection
    -of cervical infection with HR types, HR non-vaccine types, LR types, LR non-vaccine types, vaccine types and by HPV type
    -of single and multiple HPV infections
  - To assess the overall and age-stratified prevalence of normal and abnormal cytological smears for the entire population and stratified by vaccination status (if final study sample allows it)
  - To evaluate the relationship between cervical HPV infection and potential risk factors (including demographics data, lifestyle habits and medical history)

N.B. The definitions of the terms used above are as follows:
- Vaccine types: vaccine types are represented by HPV type 6, 11, 16 and 18 targeted by Gardasil®
- High-risk (HR) non-vaccine types are represented by every HR type except for HPV 16 and 18
- Low-risk (LR) non-vaccine types are represented by every LR type except for HPV types 6 and 11

5. STUDY PLAN

5.1 Study Design

Cross-sectional population-based descriptive study.

5.2 Study Site

The study will be conducted in the Italian province of Matera (covered by the LHU of Matera). The LHU is composed of several screening centres distributed in Matera province.

Approximately 16 cervical screening centres of the LHU of Matera will participate (list given in appendices). These screening centres have been selected based on: 1) the presence of computerized vaccination and screening databases; 2) the compliance to the organized cervical screening program; 3) the target population size; 4) Gardasil® use in 2009; and 5) the investigators' willingness to participate in the study.

Figure 2: Basilicata region

5.3 Study Population and period

Women from the general female population aged between 18 and 50 years residing in Basilicata region in 2011-2013.

The study population includes 2 subgroups: women aged 18-24 years and women aged 25-50 years. Only women aged 25-50 years are invited within the organized cervical cancer screening program already in place in the Basilicata region. Women aged 18-24 are invited specifically for the study.

The younger age group (18-24) is the target for a free-of-charge vaccination with Gardasil® within the frame of the regional organized HPV vaccination program. In 2011, only women aged 18-28 years may have been vaccinated with Gardasil® through the organized program (9 birth cohorts: 1983 to 1987 and 1990 to 1993). Details on potentially vaccinated birth cohorts, who may be eligible to the study, are given in table 1.

5.4 Inclusion and Non-Inclusion Criteria

5.4.1 Inclusion criteria

The inclusion criteria are the following:

- Women between 18-24 years old invited to the study
- Women between 25-50 years old invited within the frame of the organised cervical cancer screening program
- Signing an Informed Consent Form (ICF) to participate in the study

5.4.2 Non-inclusion criteria

To be included, none of the following criteria should be met:

- Virginal women
- Hysterectomized women
- Women who underwent colposcopy in the 24 months prior the enrolment visit

Table 1: Birth cohorts invited to the organized HPV vaccination program in Basilicata and age in the forthcoming year

Year of invitation to attend vaccination	Birth cohort	Age in 2007	Age in 2008	Age in 2009	Age in 2010	Age in 2011	Age in 2012
2007	1983	**24**	**25**	**26**	**27**	**28**	**29**
	1990	17	**18**	**19**	**20**	**21**	**22**
	1993	14	15	16	17*	**18**	**19**
	1996	11	12	13	14*	15	16
2008	1984	**23**	**24**	**25**	**26**	**27**	**28**
	1991	16	17	**18**	**19**	**20**	**21**
	1994	13	14	15	16	17*	**18**
	1997	10	11	12	13	14*	**15**
2009	1985	**22**	**23**	**24**	**25**	**26**	**27**
	1992	15	16	17	**18**	**19**	**20**
	1995	12	13	14	15	16	**17***
	1998	9	10	11	12	13	**14***
2010	1986	**21**	**22**	**23**	**24**	**25**	**26**
	1993	14	15	16	17*	**18**	**19**
	1996	11	12	13	14*	15	16
	1999	8	9	10	11	12	13
2011	1987	**20**	**21**	**22**	**23**	**24**	**25**
	1994	13	14	15	16	17*	**18**
	1997	10	11	12	13	14*	15
	2000	7	8	9	10	11	12

* represents the second invitation to attend the organized HPV vaccination program

Eligible for vaccination

potentially vaccinated women eligible to the study in 2011

potentially vaccinated women eligible to the study in 2012

in bold = all eligible women (age < or = 18)

5.5 Sample size considerations

The sample size has been calculated in order to allow an accurate assessment of the overall and age-stratified prevalence of HPV vaccine types (6/11/16/18) and HR HPV types other than 16 and 18.

Two age groups are considered in this study: 18-28 and 29-50 year-old women. These two age groups have been considered in order to over represent and oversample the young women (18-28) already targeted by the organized HPV vaccination program.

- **Sample size considerations for 18-28 year-old women**

Based on (1) an expected study participation rate of 22.5% [10] for 18-24 year-old women (birth cohorts 1987-1993) and (2) an expected study participation rate of 9.2% (see explanation below – table 3) for 25-28 year-old women (birth cohorts 1983-1986), we calculated the number of 18-28 year-old women residing in the province of Matera who could participate in the study during a recruitment period of one year (Table2). The number obtained is **2,221**.

In addition, based on HPV vaccination coverage provided by the LHU of Matera, the number of 18-28 year-old participating women and who could have been vaccinated can be calculated as well

(table 2).

Table 2: Expected number of study participants in one year

Birth cohorts	Age in 2011	Number of women covered by the study area	Expected participation rate (%) per year*	Expected number of participants in one year	Expected HPV vaccination coverage (%)**	Expected number of vaccinated participants
1983-1986	25-28	4345	9,2	400	52	208
1987	24	1275	22,5	287	52	149
1988	23	1259	22,5	283	~0	~0
1989	22	1135	22,5	255	~0	~0
1990	21	1191	22,5	268	78	208
1991	20	1124	22,5	253	76	197
1992	19	1065	22,5	240	61	146
1993	18	1043	22,5	235	80	188
1983-1993	18-28	**12,437**		**2,221**		1,096

* Study participation rates:
For 18-24 year-old women: 22.5% (based on the experience from the above mentioned Sicilian study [10])
For 25-28 year-old women: 9.2%, rate calculated based on the adhesion rate of the cervical screening (46% over a 3-year period) and a 60% study participation rate

** Assumption based on HPV vaccination coverage for first vaccine dose provided by the LHU of Matera

- **Sample size considerations for 29-50 year-old women**

Based on census data, 26,924 women aged between 29 and 50 years old live in the Matera area. Based on an expected study participation rate of 9.2% (see above – table 2), we calculated the number of 29-50 year-old women residing in the province of Matera and who could participate in the study during a recruitment period of one year. The number obtained is **2,477**.

- **Sample size estimates**

Based on the above mentioned study from Turin[12] in 25-70 year-old women, the prevalence of the infection with HPV vaccine types (6/11/16/18) and the prevalence of HR non-vaccine types have been reported to be 3.3% and 4.2%, respectively.

Assuming a decrease in the prevalence of HPV infection with increasing age (as observed in most studies), the prevalence is expected to be higher both in the age group 29-50 and 18-28 compared to women aged 25-70 considered in the study by Ronco et al.[12]

The following formula has been used for the calculations of the precision of the estimates:

$i = \sqrt{[(P(1-P)Z^2\alpha)/N]}$, Where $Z\alpha=1.96$ for a risk $\alpha=5\%$;

P is the prevalence of the parameter in the population;
i is the precision of the estimates
N is the sample size

The table below shows the half-width of the 95% CI of the estimated HPV prevalence (both HPV vaccine types and HPV-HR non-vaccine types). Prevalence between 3 to 25% with a two-sided $\alpha=5\%$ have been considered. Calculations have been made for 2,000 samples (for 18-28 year-old women in

order to oversample them) and 1,500 samples (for 29-50 year-old women).

Table 3: Precision of the prevalence estimation of HPV infection with a sample size (N) of 2,000 women in 18-28 age group and 1,500 in 29-50 age group.

Age groups	Sample size (N)	Prevalence of HPV (either vaccine or HR-non vaccine types in %)								Sample size+ 10% drop out/missing rate
		3	3.3	4.5	5	10	15	20	25	
18-28	2,000	0.7	0.8	0.9	1.0	1.3	1.6	1.8	1.9	2,223
29-50	1,500	0.9	0.9	1.0	1.1	1.5	1.8	2.0	2.2	1,667
18-50	3,500	0.6	0.6	0.7	0.7	1	1.2	1.3	1.5	3,890

Sample size calculation show that 2,000 and 1,500 samples are adequate minimal sample sizes in estimating prevalence of vaccine and HR-non vaccine types with good half-width of the 95% CI respectively for 18-28 and 29-50 year-old women (see table3).

Assuming a drop out/missing rate of 10% (samples not analyzable due to insufficient material for HPV testing, poor quality of the samples or loss of samples due to transport or storage problems), **2,223 women aged between 18 and 28 years old** and **1,667 women aged between 29 and 50 years old** should be included in the study. These numbers are consistent with the number of 18-50 women residing in the province of Matera who could participate in the study during a recruitment period of one year.

5.6 Study procedures

Activities to be conducted within the frame of the study are described below. In addition, the flow of data and material (samples, results…) between the different entities involved in the study (LHU, ISPO, CRO…) will be detailed in specific guidelines.

5.6.1 Invitation process

5.6.1.1 Women aged 18-24 years

The list of 18-24-year old women living in the areas served by the LHU of Matera to be invited will be generated from municipalities registries (approximately 8,092 women). All registered women aged 18-24 years will receive a study invitation letter to participate in the study describing the study objectives. A second invitation letter will be sent to the women failing to contact their screening centre 60 days after the first letter. In case of recruitment necessities women, who are still failing to respond to the second invitation letter, will be contacted by a third letter or phone call if possible.

5.6.1.2 Women aged 25-50 years

The women attending the LHU for the organized cervical cancer screening will be invited to participate to the study by the midwife/qualified staff member. The cervical cancer screening invitation letter is generated automatically from the cervical screening database.

5.6.2 Visit at LHU: Women 18-50

- **Completion of the daily report** by the midwife/qualified staff member
- **Study presentation to all eligible women:** (according to inclusion and non-inclusion criteria): the midwife/qualified staff member will present the study to the eligible women and answer any questions.

- **Signature of the ICF:** each eligible woman willing to participate will have to sign an ICF before any study procedure starts.
- **Inclusion:** eligible women consenting to participate will be included in a consecutive manner. The recruitment will stop when the expected number of women is reached.
- **Completion of Participant Form:** the Participant Form will be completed by the midwife/qualified staff member for each participating woman.
- **Cervical sampling:**

  The midwife/qualified staff member will perform a conventional Pap test (which is part of the routine cervical screening for 25-50 years old women). This sample will be used for cytological analyses.

  A second cervical sample (sample in STM- specimen transport medium) will be collected and will be sent to the ISPO central lab for HPV analyses.
- **Completion of a self-administered questionnaire:** all participating women will complete the self-administered questionnaire on site. Questionnaire data will be completely confidential. The midwife/qualified staff member will not have access to the answers

5.7 Study Duration

The expected study duration is from 2011 to 2013. It is anticipated that screening centres will recruit participants for approximately 12 to 18 months to reach the required sample size (from middle of 2011 to begin of 2013). Participant recruitment will be tracked centrally by SPMSD or delegates who will stop the recruitment when target is reached.

5.8 Sample management and analysis

5.8.1 Samples collection

- Conventional Pap tests analysis will be performed by the usual local laboratories collaborating with the LHU. Cytological results will be classified according to the Bethesda 2001 Guidelines. [13]

- For HPV analyses

The study cervical samples will be collected using the cervical sampler kit of the Hybrid Capture 2 (HC2) system. This kit contains a cervical conical brush and a vial with specimen transport medium (STM).

Samples will be labelled at the screening centres with stickers mentioning the participant number, the date of birth and the sample date. Storage will be made at the screening centres at room temperature for one week before being sent to the central laboratory for HPV analyses. Samples in STM can be stored at room temperature for up to two weeks and for an additional week between 4 and 8°C. If not tested in the first 3 weeks after collection, they can be stored at -20°C for up to three months (notice HC2). All study sample shipment will follow the specific regulation for biological specimen's shipment.

Details on sample management (sample collection, sample shipment, storage conditions) will be described in a specific laboratory manual available on site.

5.8.2 HPV analyses process

HPV analyses will be performed at a central laboratory (ISPO) in order to standardize testing

methods and practices. All HPV analyses will be performed without knowing the cytological results.

5.8.2.1 HPV testing

Samples will be tested for HPV using the Hybrid Capture 2 test (Qiagen) containing both HR and LR probes.

HC2 is based on the hybridization of synthetic RNA probes to the genomic sequence of 13 High-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and five Low-risk (6,11, 42, 43, 44) HPV types [14]. RNA-DNA hybrids are immobilized onto the test plate by capture with antibodies specific for RNA attached to the plate: DNA nucleic acid hybrids. This complex is detected with another RNA-DNA antibody conjugated to alkaline phosphatase, which results after addition of the Dioxetan substrate in chemiluminescence, and that can be measured in relative light units [15]. The intensity of the emitted light is proportional to the amount of target DNA present in the specimen, proving a semi-quantitative measure of viral load [14]. The FDA-recommended cut-off value for test-positive results is 1.0 RLU (equiv. to 1pg HPV DNA per 1ml of sampling buffer). Results from a large screening trial recently conducted in Germany indicated a sensitivity of the HC2 of 97.8% and a specificity of 95.3%[16].

For the study purpose, samples will be classified as HPV positive, borderline or negative according to the manufacturer's instructions:

- **HPV Positive:** RLU/CO ratios≥1.0
- **HPV Borderline:** RLU/CO ratios ≥0.5 and<1.0
- **HPV Negative:** RLU/CO ratios<0.5

Only women with cervical samples with RLU/CO ratios ≥1.0 will be considered as HPV positive.

5.8.2.2 HPV genotyping

For the purpose of the study, all HC2 positives, HC2 borderline and 10% of randomly selected HC2 negative samples will be genotyped using INNO-LiPA Extra test (Innogenetics).

The INNO-LiPA HPV Genotyping Extra is a line probe assay, based on the reverse hybridization principle, designed for the identification of 28 different genotypes of the human papillomavirus (HPV) by detection of specific sequences in the L1 region of the HPV genome[17].

The assay uses the proven SPF10* primer set for the highly sensitive amplification of most clinically relevant HPV genotypes. In addition, a set of primers for the amplification of the human HLA-DPB1 gene has been added to monitor sample quality and extraction, as well as the addition of UNG to the amplification mixture as a contamination prevention measure.

The assay covers all currently known high-risk HPV genotypes and probable high-risk HPV genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) as well as a number of low-risk HPV genotypes (6, 11, 40, 43, 44, 54, 70) and some additional types (69, 71, 74).

5.8.2.3 Biobank

At the central laboratory, a 100 µl aliquot of the STM sample will be removed before HPV testing (i.e. before denaturation) and stored at -80°C. These aliquots will be kept in case of potential re-testing for study purpose. The remaining STM samples will be stored at -20°C before HPV analyses are performed.

5.8.2.4 HPV analyses results

HPV analyses results (both HC2 and Lipa) will be registered at the central laboratory in an electronic database where each woman will be identified through their participant number and date of birth and sample date. This database will then be sent to the coordination centre to be merged with the

study database.

5.9 Data collected

The following data will be obtained.

5.9.1 Daily Report data

The Daily Report will be completed by each participating screening centre. Aggregated data on the total number of women invited to the cervical cancer screening program, women attending the cervical cancer program for the 25-50 age group will be collected. Aggregated data on women eligible/ineligible to the study and women enrolled/not enrolled in the study whatever their age group will be also registered.

The Daily Report will assess the participation rate among eligible women. It will provide valuable information to discuss the representativeness especially regarding the age structure of the study population versus the eligible population.

In addition, the attendance rate to the cervical cancer screening program (percentage of women seen at the screening visit for their triennal Pap test among the total number of women invited) will provide additional information to discuss the representativeness of women attending organised cervical cancer screening compared to the whole targeted population (high attendance rate is expected to be in line with a good representativeness).

5.9.2 Participant Form data

A Participant Form (PF) will be completed by the sample taker during the screening visit. This form will include the following data:

- Information on inclusion and non-inclusion criteria fulfilled
- Participant number
- Date of birth
- Date of signature of the informed consent form
- Details on samples collected and date of sampling

5.9.3 Self-administered questionnaires data

Participating women will be asked to complete a questionnaire. This questionnaire will remain strictly confidential in order to limit declaration bias as sensitive data are collected. Women will complete the questionnaire on site just after the screening visit. This completion method (on site rather than a completion at home) should increase the completion rate.

This questionnaire will collect the following data:

- Participant number
- Socio-demographic data
  - Date and Country of birth
  - Marital status
  - Education level
  - Professional status
- Risk factors for HPV infection/cervical diseases
  - Current relationship status (current partner/no current partner)
  - Smoking status (and number of cigarettes smoked for current smokers)

- Contraceptive use: past and current use
- Sexual behaviours: age at first sexual intercourse/number of sexual partners (lifetime and in the last 6 months)
- Current and past medical history: history of pregnancy/history of sexually transmitted diseases/ immuno-suppression status/history of abnormal Pap test

– HPV vaccination status
- Vaccinated/not vaccinated
- Type of vaccine (bi or quadrivalent vaccine)
- Number of doses received
- Date of last dose received
- HPV vaccination setting (public versus private)

5.9.4 Cytological data and HPV vaccination data

The study takes advantage of local registries of Basilicata's LHUs. Vaccination data will be extracted from these registries.

– HPV vaccination status
- Vaccinated/not vaccinated
- Type of vaccine (bi or quadrivalent vaccine)
- Number of doses received
- Date of doses received

– Cytological results:
- Inadequate smear
- Normal cytology
- Abnormal cytology: ASC-US/AGC/LSIL/HSIL/ASC-H/Cancer

N.B.

HPV Vaccination status will be extracted from the computerized vaccination registry. This information will also be collected through the self-administered questionnaire. Data provided by the vaccination registries will be considered the reference data since self-declared data could be prone to bias. However, the questionnaire will allow the identification of women that could have been vaccinated in private centres and consequently not registered in the LHU database.

5.9.5 HPV results

– **HC2 results**

Samples will be categorized in: HR HPV positive samples; LR HPV positive samples; HPV negative samples

– **HPV genotyping results** (Inno Lipa Extra test results)

INNO-LiPA extra test covers the following HPV types: HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82 (HR), HPV 6, 11, 40, 43, 44, 54, 70 (LR) and HPV 69, 71 and 74. HPV type(s) identified in each woman will be provided.

5.10 Potential biases and study limitations

5.10.1 Recall bias

Some data are collected through a self-administered questionnaire. Recall bias could occur. For example, women with current genital diseases at the time of the cervical screening visit could better remember past infections or exposure to HPV infection risk factors.

5.10.2 Reporting bias

Some sensitive questions are asked in the questionnaire (sexual behaviours: number of sexual partners...) and could lead to reporting bias. Refusal to answer or under-reporting (to give "politically correct" answers) could be observed. However, this bias could be limited by the fact that questionnaires are coded and self-administered.

5.10.3 Misclassification bias

Women vaccinated in private centres will not be recorded in the vaccination database from the LHU. These women could consequently appear as non HPV vaccinated. However, the number of women vaccinated in private centres is expected to be very low (because of the absence of reimbursement in private centres). HPV vaccination status will also be collected via the self-administered. Concordance between data collected in the registry and self-declared data will be assessed.

5.10.4 Selection bias

5.10.4.1 Women aged 25-50

- Representativeness of women attending the organized cervical screening program versus women from the general population

Women included are those attending the organized cervical screening program of their region on a 3-year basis. Non-compliers cannot be included in the study. Compliers and non-compliers could have different risk profiles for HPV-related diseases. Women attending the program could be better informed about cervical diseases and aware of the importance of regular cervical screening or have better access to healthcare. These women could be better followed by their physician and observe more preventive measures. If women screened in the frame of the cervical screening program are at lesser risk to develop cervical diseases, it could lead to an underestimation of the results.

One other hypothesis is that non attendees could be women followed by their private gynaecologist. These women could have a particular profile such as a higher socio-economic status and maybe a lesser risk to develop HPV-related cervical diseases. The representativeness of women attending the organized cervical screening program is debatable and the generalization of the results to the general female population should be made with caution. No significant association between participation in the screening and education, marital status or place of birth was found in a previous study on the factors associated with screening attendance in the Italian region of Turin [12]. The attendance rate to the cervical cancer screening program in areas covered by the cervical screening centres involved in the study will be collected and will be a way to discuss the representativeness of this population versus the whole female population (high attendance rate expected to be in line with a good representativeness; low attendance rate could be more in line with a low representativeness).

- Representativeness of study participants compared to women attending the cervical screening program

Eligible women who accept to be involved in the study and those who do not could have different profiles. The completion of the Daily Report will allow the assessment of the representativeness in terms of age structure. It will also allow the assessment of the participation rate among the eligible

population. A high participation rate should be in line with a good representativeness. Reasons for non participation will also be explored.

5.10.4.2 Women aged 18-24

The representativeness-related concerns are particularly important for this age group. Women accepting to participate in the study could be more informed, adopting more preventive measures than the general population, leading to an underestimation of HPV prevalence. On the opposite, they could have more risk factors than the general female population and be interested in performing cervical cancer screening. However, this could be challenged for all studies based on voluntary participation.

The participation rate will be calculated and will help to discuss the representativeness of the study population. However, there is no way with such a study design to assess the participation rate among only eligible women (women who do not participate will be both ineligible women and eligible women not willing to participate). Consequently, the participation rate will be calculated on the total number of women invited to participate in the study.

In addition, socio-demographic data collected on study participants through the self-administered questionnaire will be compared to those collected on the general female population by the national Italian Statistical Institute (ISTAT).

5.10.4.3 Women aged 18-28

Vaccinated and non vaccinated women could have different profiles. However, these differences should be limited to the age group 18-28 as women at ages 11, 14, 17 and 24 are invited to free of charge vaccination.

5.10.4.4 Women aged 29-50

Gardasil® is recommended in Italy for women up to 26 years. In Basilicata, active vaccination has been free of charge and in place since 2007. In the age group 18-28 some women will consequently be already vaccinated. In the age group 29-50 the number of vaccinated women is expected to be very low. Moreover, women already vaccinated in this age range could have specific profiles (not representative of the general population) as they could have been vaccinated on their own initiative and not been reimbursed (in private centres). Self-administered questionnaires data will allow the characterization of vaccinated women and non vaccinated women. Profiles in terms of socio-demographic characteristics, risk factors for HPV infection/HPV-related diseases and medical history could be compared to assess differences between groups.

5.10.5 Limitations

– Geographical area

This study is restricted to one area of a single Italian region. Consequently, extrapolation to the Italian territory will not be possible or should be discussed carefully.

– Breakthrough cases/vaccine failures

The unique vaccination program in place in Basilicata will allow the assessment of the HPV type prevalence in young vaccinated women (aged 18-28) from now on. However, vaccination with Gardasil® is in most cases recommended for young girls at ages 11 expected non-sexually active and consequently HPV naïve. In Basilicata, most vaccinated women to be potentially included in the age group 18-28 at this time are women vaccinated at ages 17 or 24. In this age group, a high percentage of women should be already sexually active at vaccination time. Some of them should have been already infected with HPV vaccine types before vaccination. However, as HPV status before vaccination will not be available in this study, these cases should not been misinterpreted as vaccine failures or breakthrough cases. Moreover, the definitions of suspected or confirmed vaccination failures are based on the presence of lesions or cancers due to HPV vaccine types. In this study, we will have no information on the histological results and consequently will not have the opportunity to detect vaccine failures.

5.11 Results feedback

During the study, the LHU will receive HR-HPV HC2 results for each participating women and will be responsible of communicating these results to the participants.

For the 25-50 year-old women, cytological results will be communicated to the participants by the LHU using the routine process (as defined in the frame of the organized cervical screening program). For the 18-24 year-old women, cytological results will be communicated to the participants by the LHU.

For both age , the LHU will follow a specific algorithm based on both cytological and HPV HR HC2 results and it will be responsible for all follow-up procedures.

5.12 Monitoring procedures

5.12.1 Study monitoring

Specific meetings with screening centres of the LHU will be planned before the beginning of the study. The staff involved in the study will be trained for all study procedures such as the ICF process (including full study information to study participants, ICF discussion and address any questions before signature), the sample collection (training for collection method), the storage of sample, the sample shipment, the Daily Report, the self-administered questionnaire and the PF. This training will ensure the good understanding of the protocol and the standardization of all study procedures.

Monitoring visits will be conducted by personnel properly appointed and authorized by the Sponsor. Monitoring visits aim to assess the quality of collected data and to ensure that the study is conducted and documented properly. The frequency and description of the monitoring visits will be fully detailed in the monitoring guidelines. A monitoring report will be established after each site visit and all study related communication will be recorded and archived in the study file.

5.12.2 Data Quality control

By signing this protocol the investigators agree to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that the study is conducted and data are generated in compliance with the protocol, accepted standards of good scientific conduct and all applicable government and local laws, rules and regulations relating to the conduct of the study.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.12.2.1 Quality control of cytology process

In order to assess the quality of the cytology process, a quality control will be performed by ISPO. This process will be detailed in a separate guideline. In case of discrepancies, cytological results from the LHU will be used as routinely done for the result feedback and follow-up of the participants. Cytological results from ISPO will be used for the study purposes.

5.12.2.2 Quality control of HPV testing & laboratory procedures

Detailed Standard Operating Procedures (SOP) for all steps of sample management, processing and storage will be prepared by the laboratory and will be described in a specific manual. These SOP will include detailed procedures for DNA extraction, internal quality control of the HPV testing methodology, LIPA methodology. External and internal QC on HC2 samples will be set-up and will be detailed in a laboratory manual.

5.12.3 Audits

Audits may be conducted by SPMSD or by external auditors duly appointed by SPMSD in order to ensure that the Study is performed based on the protocol, study procedures and accepted standards

of good scientific conduct and all applicable government and local laws, rules and regulations. In that case, the investigators will be informed at least 2 weeks prior to the audit conduct.

The investigators shall ensure to the auditors access to their professional premises; all study documents and participants' medical folders. The auditor shall be able to meet any person involved in the study conduct on site.

After the audit, the investigators shall take into account all comments made by the auditors and do any required corrective actions.

The investigators shall inform immediately SPMSD of any inspection done by local or European health authorities on study related activities.

5.13 Data flow and Management

Cytological and vaccination data extracted from the LHU with participant number and date of birth (without any nominative data) will be sent to the coordination centre in order to be added into the study data base.

All the study data (cytological, vaccination, HPV results, self-questionnaire, PF, Daily Report) collected will be registered into the study database at the coordination centre. These data will be identified through the participant number and date of birth.

HR HC2 HPV results, registered into the ISPO central laboratory data base, will periodically be transferred to the LHU.

A data management plan will be developed describing in details all data checks (manual and electronic) to be performed on completeness, plausibility and consistency.

5.14 Statistical Analysis Plan

All analyses will be descriptive and no formal hypothesis testing or comparison, as there are many putative confounders we cannot control for in this population-based study. The vaccination status used in the following analyses is the vaccination status communicated by the vaccination registries (not collected in the self-administered questionnaires).

5.14.1 Univariate analysis: description of the study population

5.14.1.1 Quantitative variables

The following quantitative variables will be described by their mean, standard deviation, median, quartiles and minimum/maximum.

- Age
- Number of years spent in Italy for people not born in Italy
- Duration of smoking for current smokers
- Number of years quitting smoking for ex-smokers
- Number of pregnancies
- Number of full-term pregnancies
- Age at first full-term pregnancy
- Duration of contraceptive method use
- Age at first sexual intercourse
- Number of sexual partners: lifetime/ in the last 6 months

5.14.1.2 Categorical variables

The following categorical variables will be described by the frequency and percentage.

- Age groups: 18-28, 29-50// 18-24, 25-28, 29-34, 35-39, 40-44 and 45-50
- Place of birth
- Current marital status
- Current relationship status
- Educational level
- Professional status
- Smoking status
- Intensity of smoking for current smokers
- Use of contraceptive methods
- Contraceptive methods used
- Age group at first sexual intercourse: <=11 years old, 12 years old, 13 years old, 14 years old, 15-16 years old, 17-18 years old, 19-20 years old, 21-25 years old, >=26 years old
- Number of sexual partners (lifetime and in the last 6 months): 1 sexual partner, from 2 to 4 partners, equal o more than 5 partners)
- History of genital warts (past or current)
- Current status of genital warts
- History of sexually transmitted diseases (past or current)
- Current status of sexually transmitted diseases
- Immuno-suppression status
- Reasons for immuno-supression
- History of abnormal Pap test
- Vaccination status

5.14.2 Multivariate analysis:

- Educational level by age
- Current marital status by age
- Professional status by age
- Smoking status by age
- Use of contraceptive methods by age
- Age at first sexual intercourse by age
- Number of sexual partners by age
- Vaccination status by age

Age groups considered will be 18-24/25-28/29-34-39/40-44/45-50.

5.14.3 Prevalence estimates

- The crude and age-standardized (using Italian national census data) HPV prevalence (any HPV types) and 95% CI will be given.
- The age-stratified HPV prevalence (any HPV types) and 95% CI will be given: age groups considered will be 18-28/29-50//18-24/25-28/29-34/35-39/40-44/45-50.
- The crude and age-standardized HPV prevalence and 95% CI stratified by cytological results will be given. Cytology categories include Normal smears/ ASCUS, ASC-H, AGC/LSIL/HSIL/Cancer.
- The age-stratified HPV prevalence and 95% CI will be given by cytological results. Age groups considered will be 18-24/25-28/39-34/35-39/40-44/45-50.
- The crude, age-standardized and age-stratified HPV prevalence and 95% CI will be given by vaccination status (vaccinated vs not vaccinated; per number of doses received among vaccinated women). The proportion/number of vaccinated women in the older age group (29-50) is expected to be very low (and prone to bias: it would represent women vaccinated

opportunistically). The age groups considered will be 18-28 and 29-50. Among women aged 18-28 the following age strata could be then considered if sample size allows it: 18-21, 22-23 and 24-28.

- The crude, age-standardized and age-stratified HPV prevalence and 95%CI will be given by cytological results and vaccination status if sample size allows it. Age groups 18-28 and 29-50 could be considered.
- The crude, age-standardized and age-stratified prevalence of HR types, HR non-vaccine types, LR types, LR non-vaccine types and vaccine types and 95% CI will be given overall and stratified by:
  - Cytological results. Age groups considered will be 25-50 and 18-24/25-28/29-34/35-39/40-44/45-50.
  - Vaccination status. The age groups considered will be 18-28 and 29-50. Among women aged 18-28 the following age strata could be then considered if sample size allows it: 18-21, 22-23 and 24-28.
  - By cytological results and vaccination status if sample size allows it. Age groups 18-28 and 29-50 could be considered.
- The crude, age-standardized and age-stratified prevalence of single and multiple infections and 95% CI could be given
  - For the entire population
  - By cytological results
  - By vaccination status
  - By cytological results and vaccination status
- The crude, age-standardized and age-stratified prevalence and 95% CI of cytological normal and abnormal smears will be determined
  - For the entire population
  - Stratified by vaccination status

5.14.4 Analysis of risk determinants

The association between HPV infection (dependent variables) and potential risk factors (independent variables) will be studied. Potential risk factors (independent variables) will include: age, country of birth, current marital status, current smoking status, current use of contraceptives, lifetime number of sexual partners, number of sexual partners in the last 6 months, history of abnormal Pap test, history of previous genital warts, current status and history of having a sexually transmitted infection and immuno-suppression status. Logistic regression models will be used.

Association between HPV infection and each risk factor considered above will be studied in univariable analysis in a first time.

Risk factor for which a significant association with HPV infection is found ($p<0.10$) will be then considered in the multivariable analysis.

If sample size allows it, similar analysis will be performed for HR, LR, HR non-vaccine types, LR non-vaccine types and vaccine types.

5.14.5 Other analysis

5.14.5.1 Women aged 25-50

Analysis of the representativeness especially in terms of age (through the Daily Report) of eligible women attending cervical screening, accepting to participate in the study, and those who do not. Reasons for non participation will be studied. The participation rate to the study among the eligible women will be determined. Characteristics of ineligible women will be studied (non-inclusion criteria completed…)

5.14.5.2 Women aged 18-50

Analysis to assess if study participants are representative of the general Italian female population by comparison of socio-demographic characteristics (e.g. education level, age, marital status and professional status) collected in the self-administered questionnaire and census data from the Italian National Institute of Statistics (ISTAT).

Vaccination status: the concordance between HPV vaccination status data communicated by the vaccination registries and those collected via the self-administered questionnaires will be assessed. The percentage of concordant data and the percentage of discordant results will be assessed using Kappa statistics.

5.14.5.3 Women aged 18-24

Based on the study design, it will not be possible to determine the participation rate among the eligible women from this age group (as no information on the number of eligible women will be available). The participation rate will be assessed considering as the denominator, the number of women to whom invitation letters have been sent.

Analyses will be performed based on a detailed statistical analysis plan outlining all details of the analyses to be performed.

5.15 Quality Assurance

As this is a population-based study not investigating medicinal products, the regulatory requirements for interventional studies on medicinal products (including European Directive on clinical trials) and guidelines on Good Clinical Practice (GCP) are not applicable.

The study will be conducted in accordance with Good Epidemiological Practice (see Appendices) and the Declaration of Helsinki (see Appendices). The study procedures will be performed based on the study protocol and will be documented appropriately. Data will be treated and processed in compliance with the European directive 95/46/EC regarding the data protection and all applicable Italian laws.

6. ADMINISTRATIVE AND REGULATORY REQUIREMENTS

6.1 Informed Consent Form

The local investigators will obtain written consent from each participant in the study. This will be done in a consecutive manner: each eligible woman will be asked if she agrees to participate and will be given an information letter to read. This information letter describes the study objectives and main study steps and the role as a study participant. Before signing the ICF, the investigator will explain the study, take time to answer any questions and ensure that all study related procedures are fully understood.

The ICF must be obtained before any study related procedures and must be dated and signed by the participant and investigator.

6.2 Ethics and regulatory

The study protocol, study invitation letter, information letter, ICF and questionnaire will be submitted for approval to each Research Ethic Committee of the LHU of Matera. Sites will not be initiated until the required ethics and institutional approvals have been obtained.

6.3 Data Protection

Data on women participating in the study will be protected according to the Italian privacy law regarding the protection of personal data, n. 196/03. Data will also be treated and processed in

compliance with the European directive 95/46/EC regarding the data protection.

Personal participant information collected by SPMSD from the investigator for the purpose of the study will be coded (identifiable only via a unique code number, the participant number). In addition, participants will be invited as part of the consent process to give permission for Sponsor representatives and representatives of the Ethics committees to inspect their medical records only as they relate to the study.

SPMSD is the Sponsor of this study and has its headquarters in France. Therefore, SPMSD has to comply with French data regulations as SPMSD is the "data controller" and bears the final responsibility in reference to the treatment of the data. All relevant study documentation (e.g. protocol, ICF, PF) will be submitted for authorization to the "Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé" (CCTIRS) and the French National Commission of Computerised data and Freedom ("Commission National de l'Informatique et des Libertés, CNIL").

6.4 Insurance

An insurance policy has been contracted by the Sponsor to cover the study-related injuries occur to the participants.

6.5 Investigator responsibilities

6.5.1 Confidentiality

By signing this protocol, the Investigators affirm to SPMSD that information furnished to them by SPMSD will be maintained in confidence and will be only revealed to study collaborators, affiliated institution(s) and employees under an appropriate understanding of confidentiality with such study collaborators, affiliated institution(s) and employees. The Investigators agree that, subject to local regulations and ethical considerations, a SPMSD or delegated CRO representative or any relevant ethics committee, regulatory agency have the right to access, to monitor, inspect or audit any of the individual participants records, the main study database, regulatory documents, reports and correspondence relating to the management of the study.

6.5.2 Compliance to Protocol and Law

By signing this protocol, the Investigators agree to conduct the study in an efficient and diligent manner in accordance with this protocol and local laws, rules and regulations including the latest version of the declaration of Helsinski (see Appendices) and the guidelines of Good Epidemiology Practices (see Appendices).

By signing this protocol, the Investigators agree also to ensure that the study data collected in the questionnaire will be recorded accurately, promptly and legibly.

7. STUDY COMMITTEES

7.1 Steering Committee

The role of the Steering Committee (SC) is to ensure and coordinate the practical undertaking of the study and to supervise it through regular meetings (to provide advice on the protocol including aims, study design, sample size calculations, data management plan, statistical analysis plan, questionnaires, reports etc.). In particular, the SC will be in charge of contributing to the writing of the study protocol and ensuring that it is applied throughout the entire study period. The SC will coordinate all activities related to the study in accordance with the study protocol, will supervise the

data management and statistical analysis procedures, and will supervise and review the final report before submission to the Advisory Board (AB). Steering Committee members are given in the table below:

Table 4: Steering Committee members

Pasquale Silvio Anastasio (Principal Investigator for cervical screening) **Espedito Antonio Moliterni** (Principal Investigator for vaccination)	**Azienda Sanitaria Locale di Matera**	Dipartimento Materno Infantile - Ospedale "Madonna delle Grazie" C.da Cattedra Ambulante - 75100 Matera, Italy Dipartemento di Prevenzione Via Montescaglioso, 20 Matera, Italy
Francesca Carozzi (Scientific Coordinator) **Donella Puliti** (Data Manager & Statistician)	**Istituto per lo studio e la prevenzione oncologica**	Istituto per lo studio e la prevenzione oncologica 2 Via Cosimo il Vecchio 50139 Firenze, Italy
Rocco Alessandro G. Maglietta	**Istituto di ricovero e cura a carattere scientifico - Centro di Riferimento Oncologico della Basilicata**	Direzione Generale Via Padre Pio, 1 85028 Rionero in Vulture (PZ), Italy
Sergio Schettini	**Azienda Ospedaliera San Carlo di Potenza**	Dipartimento di Ostetricia e Ginecologia Via Potito Petrone, 1 85100 - Potenza, Italy
Laurence Serradell (Epidemiological Project Manager) **Samantha Atrux-Tallau** (Epidemiological Projects Coordinator)	**SPMSD Epidemiology Unit - Europe**	Sanofi Pasteur MSD SNC 8, rue Jonas Salk 69367 - Cedex 07 Lyon, France
Emilia Perinetti (Clinical & Epidemiology Manager)	**SPMSD Medical Department- Italy**	SPMSD Medical and Scientific Department Via degli Aldobrandeschi, 15 00163 – Rome, Italy

7.2 Advisory Board

The role of Advisory Board is to validate through regular meetings the protocol and the interim/final results and reports of the study as well as any publications related to the study.

Table 5: Advisory Board members

Paolo Bonanni	University of Florence Dept of Public Health and Epidemiology Viale Morgagni 48 50134 Florence, Italy
Marta Ciofi degli Atti	Ospedale Pediatrico Bambino Gesù P.za S. Onofrio, 4 - 00165 Rome, Italy.
Xavier Castellsagué	Institut Català d'Oncologia Epidemiology and Cancer Registration Unit Avda. Gran Via, s/n km 2,7 08907 L'Hospitalet de Llobregat, Barcelona, Spain
Thomas Iftner	University Hospital of Tuebingen Section Experimental Virology Elfriede-Aulhorn Strasse 6 72076 Tuebingen, Germany
Guest	
Pier Luigi Lopalco	European Centre for Disease Prevention and Control (ECDC) SE-171 83 Stockholm, Sweden

8. PUBLICATION RULES

Study and all the results arising from the Study are and remain SPMSD exclusive and sole property. In the interest of scientific openness and in order to inform the wider medical and scientific community, SPMSD and the investigators are jointly committed to submit for publication to an (inter)national conference or a reputable peer-reviewed journal an abstract/manuscript relating to the Study. Publication rules are defined in the study financial agreement in the corresponding section.

9. STUDY DOCUMENTATION AND ARCHIVING

Study documentation includes all questionnaires, laboratory reports, data correction forms, source documents, monitoring logs, sponsor / CRO / investigators' correspondence, Ethics Committee / regulatory documents (e.g., confidentiality agreement, signed protocol and amendments; inventory list, shipping letter, etc.), and any other reports or records of procedures performed in accordance with the protocol.

Study documentation should be retained in secure archives by both individual investigators and SPMSD for at least 5 years after final report or first publication of study results according to internal procedures.

10. REFERENCES

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11. APPENDICES

11.1 List of screening centres

- Ferrandina
- Salandra
- Bernalda
- Grassano
- Irsina
- Matera 1
- Matera 2
- Miglionico
- Montescaglioso
- Policoro 1
- Policoro 2
- Pomarico
- Stigliano
- Tinchi (zone hospital for Pisticci)
- Tricarico
- Hospital Obstetrical clinics of Matera

11.2 Participant Form

sanofi pasteur MSD
vaccines for life

Study GDS02E

Monitoring HPV Type Prevalence in the Post-vaccination Era in Women Living in the Basilicata Region, Italy

Sponsor: Sanofi Pasteur MSD *8 rue Jonas Salk 69367 LYON CEDEX 7-France*
Tel: +33 437 284 000

Participant Form

Contact ERA: Name |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|
Tel |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

INSTRUCTIONS

- Completion and signature only by the dedicated staff member authorised.
- Complete legibly (preferably in capital letters) the Participant Form with a blue or black ball point pen.
- Check that all the inclusion and non inclusion criteria are fulfilled before IGF/signature. All participants reported should be eligible.
  INCLUSION CRITERIA
  1: Women between 18-24 years old invited to the study or Women between 25-50 years old invited within the frame of the organised cervical cancer screening program
  2: Signing an Informed Consent Form (ICF) to participate in the study
  NON INCLUSION CRITERIA
  3: Virginal women
  4: Hysterectomized women
  5: Women who underwent colposcopy in the 24 months prior the enrolment visit
- Participant number: consisting of 6 digits (Site number: 2digits and Inclusion number: 4digits = chronological order of participant inclusion)
- If "Criteria fulfilled?" is ticked YES, complete the "Inclusion number", "Cervical samples", Questionnaire data. Otherwise, report the "Criteria number(s)" not fulfilled and leave the "Cervical Samples" box empty.
- Do not remove any Participant Form pages.

Please send the completed form with all pages (original & duplicate) to the LHU Vaccination Unit.

Confidential – For Screening Centres & LHU Vaccination Unit	GDS02E	Participant Form	Site n° ⌊_⌊_⌋	P. 1

Name Surname	Birth date ICF date	Criteria Inclusion N°	Cervical samples	Q¤	N°
Name ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ Surname ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋	Birth date ⌊_⌊_⌋⌊_⌊_⌋⌊_⌊_⌊_⌊_⌋ ICF date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	Criteria* fulfilled? YES ☐ ⇒ Inclusion N° ⌊_⌊_⌊_⌋ NO ☐ ⇒ Criteria N° ⌊_⌊_⌋	For cytological analysis (Pap smear): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋ For HPV analysis (STM Sample): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	YES ☐ NO ☐	1
Name ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ Surname ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋	Birth date ⌊_⌊_⌋⌊_⌊_⌋⌊_⌊_⌊_⌊_⌋ ICF date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	Criteria* fulfilled? YES ☐ ⇒ Inclusion N° ⌊_⌊_⌊_⌋ NO ☐ ⇒ Criteria N° ⌊_⌊_⌋	For cytological analysis (Pap smear): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋ For HPV analysis (STM Sample): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	YES ☐ NO ☐	2
Name ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ Surname ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋	Birth date ⌊_⌊_⌋⌊_⌊_⌋⌊_⌊_⌊_⌊_⌋ ICF date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	Criteria* fulfilled? YES ☐ ⇒ Inclusion N° ⌊_⌊_⌊_⌋ NO ☐ ⇒ Criteria N° ⌊_⌊_⌋	For cytological analysis (Pap smear): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋ For HPV analysis (STM Sample): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	YES ☐ NO ☐	3
Name ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ Surname ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋	Birth date ⌊_⌊_⌋⌊_⌊_⌋⌊_⌊_⌊_⌊_⌋ ICF date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	Criteria* fulfilled? YES ☐ ⇒ Inclusion N° ⌊_⌊_⌊_⌋ NO ☐ ⇒ Criteria N° ⌊_⌊_⌋	For cytological analysis (Pap smear): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋ For HPV analysis (STM Sample): YES ☐ NO ☐ date ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋	YES ☐ NO ☐	4

Q¤ : Self administered Questionnaire

*INCLUSION CRITERIA
Women between 18-24 years old invited to the study or women between 25-50 years old invited within the frame of the organised cervical cancer screening program [1]
Signing an informed consent form to participate in the study [2]

*NON INCLUSION CRITERIA
Virginal women [3]
Hysterectomized women [4]
Women who underwent colposcopy in the 24 months prior the enrolment visit [5]

I undersigned, ... hereby certify that all the data recorded in this Participant form are consistent with source data.

Date: ⌊_⌊_⌋⌊_⌊_⌋2 0⌊_⌊_⌋

Signature:

Original without Name/Surname: for Data Management - Duplicate: for LHU Vaccination Unit

11.3 Self-administered questionnaire

Study GDS02E	PARTICIPANT NUMBER	|_|_|_| - Site number |_|_|_|_|_| Inclusion number	Page 1

Questionnaire

Thank you for taking the time to complete this questionnaire
There are no correct or wrong answers but it is important that you answer each question accurately and honestly.

Please note that your answers will be kept ***strictly confidential*** *(The medical personnel will not have access to your answers)*

Demography		
1	Where were you born? ☐ In Italy ☐ In another country..... ➤	Please specify ☐ Other European country, please specify:..... ☐ Africa ☐ Asia ☐ North America ☐ South America ☐ Oceania ➤ Since how many years have you lived in Italy? |_|_|
2	What is your current marital status?	☐ Single ☐ Married ☐ Divorced / separated ☐ Widowed
3	What is your highest level of education at this time?	☐ No title (Nessun titolo di studio) ☐ Primary school (Licenza elementare) ☐ Secondary school (Licenza media) ☐ High-school diploma (Diploma di instruzione secondaria superiore: Maturità) ☐ University degree (Diploma di Laurea) ☐ Higher degree (Dottorato di ricerca/specializzazione post-Laurea/Master universitario) ☐ Other, specify:.....
4	What is your current professional status?	☐ Employed (Già occipato) ☐ Looking for a job (in cerca con esperienza/ in cerca senza esperienza) ☐ Housewife (Casalingua) ☐ High school Student (studente) ☐ University Student (studente) ☐ Retired (ritirato del lavoro) ☐ Other, specify:.....

Study GDS02E	PARTICIPANT NUMBER	|_|_|_| - |_|_|_|_| Site number / Inclusion number	Page 2

Smoking habits

5 Do you smoke currently?

☐ Yes ➢ How long have you been smoking?
|_|_| months or |_|_| years
Your frequency:
☐ < 7 cigarettes per week
☐ 1-9 cigarettes per day
☐ 10-20 cigarettes per day
☐ > 20 cigarettes per day

☐ No, have quit smoking ➢ How long have you given up smoking?
|_|_| months or |_|_| years

☐ No, have never smoked

Pregnancy / Sexual habits

6 Have you ever been pregnant?

☐ Yes ➢ Please specify
How many times |_|_|
How many full-pregnancies |_|_|
Age at first full-term pregnancy |_|_|

☐ No

7 Have you ever used a contraceptive method?

☐ Yes ➢ Please specify your current method(s) used:
- Hormonal contraceptives ☐ Yes ☐ No
  Time of use: |_|_| years or |_|_| months (if < 1 year)
- Intrauterine Device ☐ Yes ☐ No
  Time of use: |_|_| years or |_|_| months (if < 1 year)
- Partner vasectomy ☐ Yes ☐ No
- Condom ☐ Yes ☐ No
- Rhythm method ☐ Yes ☐ No
- Other ☐ Yes ☐ No, specify: .....

➢ Please specify your past method(s) used:
- Hormonal contraceptives ☐ Yes ☐ No
  Time of use: |_|_| years or |_|_| months (if < 1 year)
- Intrauterine Device ☐ Yes ☐ No
  Time of use: |_|_| years or |_|_| months (if < 1 year)
- Partner vasectomy ☐ Yes ☐ No
- Condom ☐ Yes ☐ No
- Rhythm method ☐ Yes ☐ No
- Other ☐ Yes ☐ No, specify: .....

☐ No

Study GDS02E	PARTICIPANT NUMBER |_|_|_| - Site number |_|_|_|_|_| Inclusion number	Page 3

Research has shown that the number of sexual partners is one of factor of getting infected with HPV. We would like to ask you some several questions about your sexual behaviour. It is important that you answer accurately each question.

8	How old were you at your first sexual intercourse?	|_|_| years
9	How many sexual partners did you have in the last 6 months?	☐ 0 ☐ 1 ☐ 2 to 4 ☐ ≥ 5
10	How many sexual partners did you have in your lifetime?	☐ 1 ☐ 2 to 4 ☐ ≥ 5

Current and past medical history

11	*Genital warts:*	
	➢ Do you have genital warts currently?	☐ Yes ☐ No ☐ Don't know
	➢ Have you already had genital warts in the past?	☐ Yes ☐ No ☐ Don't know
12	*Sexually transmitted disease (ex. Chlamydia, Herpes, Trichomonas, Gonorrhea, HIV, Syphilis):*	
	➢ Do you have a sexually transmitted disease currently?	☐ Yes ☐ No ☐ Don't know
	➢ Have you already had a sexually transmitted disease in the past?	☐ Yes ☐ No ☐ Don't know
13	Are you currently <u>immunocompromised</u>*? ☐ Yes ☐ No	➢ Specify the reason: ☐ AIDS ☐ Transplant / Immunotherapy ☐ Chemotherapy ☐ Other, specify:.....
	* *"<u>Immunocompromised</u>": having an immune system impaired by disease or treatment*	
14	Did you have any Pap test in your life? ☐ Yes ☐ No	➢ Was one of Pap tests abnormal? ☐ Yes ☐ No → Have you been treated? ☐ Yes ☐ No

HPV vaccination History

15	Have you been vaccinated against human Papillomavirus? ☐ Yes ☐ No	
	Have you been vaccinated in Matera area? ☐ Yes ☐ No, please complete questions hereafter....	➢ Which vaccine did you receive? ☐ Gardasil *(quadrivalent vaccine: vaccine administered in the frame of the organised HPV vaccination program in Basilicata)* ☐ Cervarix *(bivalent vaccine)* ☐ Don't know
		➢ How many doses did you receive? ☐ 1 ☐ 2 ☐ 3 ☐ Don't know
		➢ When did you receive the last dose? *(if month unknown, please report the year)* |_|_|/|_|_|_|_| mm / yyyy ☐ Don't know
		➢ Where have you been vaccinated? ☐ In private center ☐ In public center

Thank you for your participation
Please return the questionnaire in the enclosed envelope

11.4 Good epidemiological practice

Guidelines for Good Pharmacoepidemiology Practices (GPP)
Initially issued: 1996

Revision 1: August 2004

Revision 2: April 2007

Introduction
Pharmacoepidemiologic studies provide valuable information about the health effects of healthcare products. The ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) are intended to assist investigators with issues pertaining to the planning, conduct, and evaluation of Pharmacoepidemiologic research. The first revision, in 2004 revised and superseded the Guidelines for Good Epidemiologic Practice (GEP) developed in 1996. In that revision, the scope of the guidelines was broadened geographically and conceptually, to reflect ISPE's international membership, to include risk management and pharmacoeconomic activities, and to address more clearly the role of epidemiologic studies from industry and regulatory perspectives. Specifically, the 2004 revision provided guidance on regulatory reporting requirements as they relate both to individual cases and to aggregate data (see, VI. Adverse Event Reporting). The focus of the second revision has been on the use and communication of statistical measures and to add clarification to specific items throughout the document.

ISPE recognizes that Pharmacoepidemiologic research-the study of the use and effects of healthcare products (e.g., including pharmaceuticals, devices and vaccines)-has expanded to include clinical, economic and other health outcomes, requiring study methods that were not covered in previous guidelines. Pharmacoepidemiology is being used increasingly to evaluate health care systems, interventions, and health-related behaviors. Pharmacoepidemiology is the scientific backbone of therapeutic risk management-the process of assessing a product's benefits and risks, and developing, implementing, and evaluating strategies to enhance the overall balance of such benefits and risks. These guidelines are intended to address these activities and other Pharmacoepidemiologic studies.

The Guidelines for Good Pharmacoepidemiology Practices (GPP) have been adapted from a document prepared by the Chemical Manufacturer's Association Epidemiology Task Group.[1] When appropriate, we have (with permission) retained the text of that document. In addition, readers should also consult the ICH Guideline on Good Clinical Practice (GCP) (http://www.emea.eu.int/pdfs/human/ich/013595en.pdf) and the Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Ethical Review of Epidemiological Studies (http://www.cioms.ch/frame_1991_texts_of_guidelines.htm).

The GPP address the following areas:

- Protocol Development
- Responsibilities, Personnel, Facilities, Resource Commitment, and Contractors
- Study Conduct
- Communication
- Adverse Event Reporting
- Archiving

A. Goals
The GPP propose minimum practices and procedures that should be considered to help ensure the

quality and integrity of Pharmacoepidemiologic research, and to provide adequate documentation of research methods and results. The GPP do not prescribe specific research methods, nor will adherence to guidelines guarantee valid research.

The GPP have the following specific goals:

1. To assist researchers in adhering to good Pharmacoepidemiologic research principles, including the use of Pharmacoepidemiologic studies for risk management activities.

2. To promote sound Pharmacoepidemiologic research by encouraging rigorous data collection, analysis, and reporting.

3. To provide a framework for conducting and evaluating Pharmacoepidemiologic studies.

4. To facilitate the appropriate utilization of technical resources by promoting careful study design and planning of study conduct.

B. Scope and Application

The GPP are intended to apply broadly to all types of Pharmacoepidemiologic research, including feasibility studies, validation studies, descriptive studies, as well as etiologic investigations, and all of their related activities from design through publication.

Therapeutic risk management activities provide a formal framework in which medicine, Pharmacoepidemiology and public health are integrated in the development and life-cycle management of healthcare products. Pharmacoepidemiology is the core science of risk assessment and the evaluation of the effectiveness of risk minimization interventions. As such, the GPP also support risk management activities.

II. Protocol Development

Each study should have a written protocol. A protocol should be drafted as one of the first steps in any research project, and the protocol should be amended and updated as needed throughout the course of the study. The protocol should include the following elements:

A. A descriptive title and version identifier (e.g., date);

B. The names, titles, degrees, addresses, and affiliations of all responsible parties, including the principal investigator, co-investigators, and a list of all collaborating primary institutions and other relevant study sites;

C. The name and address of each sponsor;

D. An abstract of the protocol;

E. The proposed study tasks, milestones, and timeline;

F. A statement of research objectives, specific aims, and rationale;

Research objectives describe the knowledge or information to be gained from the study. Specific aims list key exposures and outcomes of interest, and any hypotheses to be evaluated. The protocol should distinguish between a limited number of a priori research hypotheses and hypotheses that are generated based on knowledge of the source data. The rationale explains how achievement of the specific aims will further the research objectives.

G. A critical review of the literature to evaluate pertinent information and gaps in knowledge;

The literature review should describe specific gaps in knowledge that the study is intended to fill. The literature review might encompass relevant animal and human experiments, clinical studies, vital

statistics, and previous epidemiologic studies. The literature review should also cite the findings of similar studies, and the expected contribution of the current study.

H. A description of the research methods, including:

1. The overall research design, strategy, and reasons for choosing the proposed study design;

Research designs include, for example, case-control, cohort, cross-sectional, nested case-control, safety trials or hybrid designs.

2. The population or sample to be studied;

The population is defined in terms of persons, place, time period, and selection criteria. The rationale for the inclusion and exclusion criteria and their impact on the number of subjects available for analysis should be described. If any sampling from a base population is undertaken, description of the population and details of sampling methods should be provided.

3. The strategies and data sources for determining exposures, health outcomes, and all other variables relevant to the study objectives, such as potential confounding variables and effect measure modifiers;

Data sources might include, for example, questionnaires, hospital discharge files, abstracts of primary clinical records, electronic medical records, ad hoc clinical databases, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, or exposure/disease registries. Use validated instruments and measures whenever such exist, and describe the validation method. If data collection methods or instruments will be tested in a pilot study, plans for the pilot study should be described. Any expert committees and evaluation procedures to be used to validate diagnosis should be described.

4. Clear operational definitions of health outcomes, exposures, and other measured risk factors as well as selection criteria and comparison groups;

An operational definition is one that can be implemented independently using the data available in the proposed study. For example "pneumocystis carinii pneumonia, episode" is not an operational definition; a better description would be "hospitalization with a primary discharge diagnosis of ICD-9-CM code 136.3."

5. Projected study size, statistical precision, and the basis for their determination;

Describe the relation between the specific aims of the study and the projected study size in relation to each outcome. In most circumstances it is desirable to express study goals in terms of precision sought for study estimates rather than statistical power. For safety studies, it may be useful to specify the sample size that can minimally detect a pre-specified risk with a pre-specified power, For example, "the study has an 80% power to detect a relative risk of 3 or greater for drug x compared to treatment with other drugs commonly used in this condition."

6. Methods used in assembling the study data;

This should include a description of, or reference to any pre-testing procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders, or data entry personnel. This should also include procedures for linkage and data mining of administrative databases.

7. Procedures for data management;

Describe data management and statistical software programs and hardware to be used in the study. Describe data preparation and analytical procedures as well as the methods for data retrieval and collection. Methods for data analysis;

Data analysis includes all the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, or modify raw data. Data analysis comprises comparisons and methods for analyzing and presenting results, categorizations, and procedures to control sources of bias and their influence on results, e.g., possible impact of biases due to selection bias, misclassification, confounding, and missing data. The statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, for instance, should be presented. Any sensitivity analyses should be described.

8. A description of quality assurance and quality control procedures for all phases of the study;

Mechanisms to ensure data quality and integrity should be described, including, for example, abstraction of original documents, extent of source data verification, and validation of endpoints. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups.

9. Limitations of the study design, data sources, and analytic methods;

At a minimum, issues relating to confounding, misclassification, selection bias, generalizability, and random error should be considered. The likely success of efforts taken to reduce errors should be discussed.

I. A description of plans for protecting human subjects;

This section should include information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects, and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study. Conditions under which a clinical trial would be terminated for ethical reasons (stopping rules) should be described. Procedures for monitoring results should be described, and the use of a Data Safety Monitoring Board (DSMB) for clinical trials should be considered for this purpose. The need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the requirement of informed consent should be considered in accordance with local law. See Section IV A.

J. A description of plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication;

There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g., results pertaining to the safety of a marketed medication). Authorship should follow guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/). See also, Section V. Communication. The Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/statement/revisedstatement.htm) refers to randomized studies, but provides useful guidance applicable to nonrandomized studies as well.

K. Resources required to conduct the study;

Describe time, personnel, services (e.g. database access), and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.

L. Bibliographic references;

M. Dated amendments to the protocol.

Significant deviations from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, along with the rationale, should be documented in writing. Any changes made after data analysis has begun should be documented as such and the rationale provided.

III. Responsibilities, Personnel, Facilities, Resource Commitment, and Contractors

A. Responsibilities

The organization(s) and individual(s) conducting and sponsoring the research shall be fully responsible for the research. The relationship, roles, and responsibilities of the organizations and/or individuals conducting and sponsoring the study should be described.

For safety studies sponsored and conducted by a pharmaceutical company, the individuals responsible for Pharmacoepidemiologic research, along with the type of expertise and autonomy in conducting the research, should be stated clearly. For projects sponsored by one organization (such as a pharmaceutical company or, government agency) but implemented by another (e.g., an academic institution or a contract research organization-CRO), responsibility for scientific integrity is shared by the collaborating institutions (e.g, sponsor, the principal investigator conducting the study, the senior qualified epidemiology staff within the CRO and the organization that employs the principal investigator). In such situations of shared responsibility, contractual arrangements should include a timeline for study completion and contingency plans if the timeline cannot be met. In particular, the contract should delineate the roles and responsibilities to be assumed by the study sponsor and the contractor(s) in communicating various aspects of the study as well as data access, ownership and archiving.

B. Personnel

Personnel engaged in epidemiologic research and related activities should have the education, training, or experience necessary to perform the assigned functions competently. The organization should maintain a current summary of training and experience of these personnel. A list of individuals engaged in or supervising activities should be maintained and updated periodically with current job titles.

C. Facilities

Adequate physical facilities shall be provided to all those engaged in epidemiologic research and related activities. Sufficient resources, e.g., office space, relevant equipment, and office/professional supplies, shall be available to ensure timely and proper completion of all studies. Suitable storage facilities shall be available to maintain technical records in a secure and confidential environment in compliance with local regulations.

D. Resource Commitment

Sufficient commitment shall be made at the beginning of each study to ensure its timely and proper completion.

E. Contractors

For the purposes of ensuring and documenting the contractor's conformance with the GPP, it is recommended that the study sponsor have the right during the course of the study, and for a reasonable period following completion of the study, to inspect the contractor's facilities, including equipment, technical record, and records relating to the work conducted under the sponsor's contract. The nature of the audit, including procedures that ensure patient confidentiality, should be agreed upon at the outset of any contract.

IV. Study Conduct

The principal investigator shall be responsible for the overall content of the individual research project, including the day-to-day conduct of the study, interpretation of the study data, and preparation and publication of the final report. These responsibilities extend to all aspects of the study, including periodic reporting of study progress as well as quality assurance.

The unusual decision to terminate a study prematurely should be taken with great caution, and should be based on good scientific and ethical reasons and documented in writing. There may be rare instances in which administrative reasons require study termination. Such decisions should be independent of any study results. Investigators and sponsors should specify and agree in advance about the circumstances under which the study could be terminated early. Included should be a mechanism for resolution of any disagreement.

A. Protection of Human Subjects

Approval by an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or other appropriate body, should be obtained for all research involving human subjects. Informed consent will be needed when the research imposes a risk for patients. Informed consent also is normally required if the study requires data containing personal identifiers. Studies conducted entirely using administrative databases or records that do not contain any personal identifiers, or which meet certain other criteria, may require only abbreviated review or may not require formal review, at the discretion of the IRB/IEC.

Investigators shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations. Whenever feasible, study files should be coded and stripped of personal identifiers, and code keys stored separate from study files. All personnel with access to data containing personal identifiers will sign a pledge to maintain the confidentiality of study subjects, and will maintain an ability to verify the origin and integrity of data sets from which personal identifiers will have been removed. For additional information, please consult the ISPE guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health (http://www.pharmacoepi.org/resources/privacy.cfm). Blood and serum sample collections stored after completion of clinical studies are a valuable resource. However, protecting confidentiality in such data requires special consideration and investigators are encouraged to consult guidelines developed by the NHLBI.[2]

B. Data Collection, Management, and Verification

All data collected for the study should be recorded accurately, promptly, and legibly. The individual(s) responsible for the integrity of the data, computerized and hard copy, shall be identified, and shall have the education, training, and experience to perform the assigned tasks.

All procedures used to obtain, verify and promote the quality and integrity of the data should be recorded in sufficient detail so that others can replicate them. A historical file of these procedures shall be maintained, including all revisions and the dates of such revisions. Any changes in data entries shall be documented.

Security of the data should be maintained at all times. Access should be limited to authorized individuals. Control systems, such as document encryption, should be used to ensure the authenticity, integrity and confidentiality of electronic records when transmitted over open networks (e.g., the internet). Adequate back up of the data should be maintained throughout the course of the study.

C. Analysis

1. A clearly defined statistical analysis plan with statistical procedures should be presented

2. All data management and statistical analysis programs and packages used in the analyses should be documented and archived. Reasonable effort should be made to document and validate interim steps in the analysis.

3. The analysis should be directed toward the unbiased estimation of the epidemiologic parameters of interest (e.g., risk or rate differences, risk or rate ratios). The precision of effect estimates should be quantified separately using confidence intervals.

Interpretation of statistical measures, including confidence intervals, should be tempered with appropriate judgment and acknowledgements of potential sources of error and limitations of

the analysis, and should never be taken as the sole or rigid basis for concluding that there is or is not a relation between an exposure and outcome. Sensitivity analyses should be conducted to examine the effect of varying the study population inclusion/exclusion criteria, the assumptions regarding exposure, potential effects of misclassification, unmeasured confounders, and the definitions of potential confounders and outcomes on the association between the a priori exposure of interest and the outcome(s).

D. Study Reports

Describe need and purpose of interim report when applicable. If required, the issuance of such reports must be pre-specified in the study protocol.

Completed studies shall be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

The final report shall include at minimum:

1. A descriptive title;
2. An abstract;
3. Purpose (objectives) of the research, as stated in the protocol;
4. The names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators;
5. Name and address of each sponsor;
6. Dates on which the study was initiated and completed;
7. Introduction with background, purpose, and specific aims of the study;
8. A description of the research methods, including:

    a. source population and selection of study subjects;
    b. data collection methods and, if questionnaires or surveys are involved, complete copies (including skip patterns);
    c. transformations, calculations, or operations on the data;
    d. statistical methods used in data analyses.

9. A description of circumstances that may have affected the quality or integrity of the data; Describe the limitations of study approach and the methods used to address them (e.g., response rates, missing or incomplete data)

10. Analysis of the data; Include sufficient tables, graphs, and illustrations to present the pertinent data and to reflect the analyses performed. Epidemiologic parameters (e.g., risks, rates, risk or rate differences, risk or rate ratios) are the most typical epidemiologic measures to report. Both unadjusted and adjusted results should be presented. Effect measures should not be described as "significant" or "not significant." Precision of estimates should be quantified using confidence intervals. Estimation is preferable to tests of statistical significance. Confidence intervals communicate both the strength of the relationship and the precision of the measure and are therefore more informative than point estimates accompanied by p-values.

11. A statement of the conclusions drawn from the analyses of the data;

12. A discussion of the implication of study results; Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research. Inferences about causal effects should be based on a variety of factors that should be explored in the

discussion section. These factors include strength of relationship, temporal relationship, biological mechanism, plausibility of alternative theories, biases, confounding, precision, and others.

13. References.

V. Communication

Each organization and its advisory board, if there is one, shall predetermine procedures under which communications of the intent, conduct, results, and interpretation of an epidemiologic study will occur, including what function individuals associated with the research must fulfill. These individuals should include the principal investigator, study director, and/or the sponsor. This procedure may be documented in the form of a company standard operating procedure, in the study protocol, or through contractual agreement.

ISPE encourages communicating estimates of epidemiologic measures quantitatively in the results section, generally by using point estimates and confidence intervals, either directly or graphically. It is useful in reporting results of safety studies to include both the relative and absolute risk estimates. Inferences about causal effects should be based on a variety of factors that should be explored in the discussion section. These factors include strength of relationship, temporal relationship, biological mechanism, plausibility of alternative theories, biases, confounding, precision, and others. Investigators should not make inferences about causation based solely on the outcome of a test of significance (e.g., a p-value or a statement about the confidence interval including or not including the null value). See also: Guidelines established by the International Committee of Medical Journal Editors, http://www.icmje.org/, section IV, and CONSORT Statement, http://www.consort-statement.org/Statement/examples20.htm.

There is an ethical obligation to disseminate findings of potential scientific or public health importance. Scientific peers shall be informed of study results in a timely fashion by publication in the scientific literature and presentations at scientific conferences, workshops, or symposia. Presentations at meetings should not be considered as a substitute for publication in the peer-reviewed literature. Authorship of study reports should follow the guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Potential conflicts of interest, financial and non-financial, should be disclosed. Agreement to adhere to these guidelines should be described in the protocol.

Finally, research sponsors (government agencies, private sector, etc.) shall be informed of study results in a manner that complies with local regulatory requirements. Sources of research funding should always be acknowledged, whether results are presented orally or in writing.

VI. Adverse Event Reporting From Pharmacoepidemiology Studies

The findings of epidemiologic studies of health risks associated with healthcare products must be reported by pharmaceutical sponsors to regulatory agencies according to local and international requirements. Depending on the nature of the result and the regulations in effect, the result may need to be reported in an expedited manner (e.g. as "new relevant safety information"). In any case, results of all epidemiologic studies of healthcare product safety should be included by companies in their periodic aggregated regulatory reports, such as Periodic Safety Update Reports (PSUR) and similar regulatory documents. Relevant regulatory guidance documents should be consulted.

It is useful to distinguish reporting of aggregate results from epidemiologic studies (i.e., study reports) from the reporting of individual adverse drug events (ADEs). Pharmacoepidemiologic studies are usually designed to assess the relation between certain exposures and health outcomes based on aggregate analyses. In such studies, particularly in case-control studies and others that may be based on retrospectively collected data, it is generally not possible or appropriate for companies to assess the causality of individual cases, although aggregate analysis of a series of study cases might identify a newly recognized adverse effect. In studies where there is no assessment of causality for individual cases, sponsors should report aggregate findings as study reports, not as individual spontaneous reports.

In prospective clinical trials where clinicians are systematically asked to report adverse events and to indicate whether each event could have been related to treatment, serious events indicated by the investigator to be at least possibly related are reportable.

Individual case reporting may be appropriate in prospective cohort studies aimed at elucidating information about a specific ADE (e.g., a drug safety registry). It is appropriate, therefore, to consider the potential value of, and necessity for, collecting such data when designing the study, taking into account existing safety experience with the drug being studied and the objectives of the study.

The principal aim of expedited reporting of individual ADEs from studies to regulatory authorities is to contribute to recognition of unexpected effects (e.g., "signal detection"). In general, an individual study case should be reported on an expedited basis by pharmaceutical sponsors when, after an evaluation of the circumstances of the individual patient, the adverse event is considered serious and unexpected (unlabeled) and there is a reasonable possibility that a healthcare product may have contributed to the occurrence of the adverse event. Expedited individual case reporting is generally required when all of the following conditions obtain: 1) the study prospectively gathers data on individual patients, 2) the study involves direct contact with patients, 3) study personnel are trained on gathering and reporting adverse events and determining whether events might be considered "expected" for a specific product, 4) a serious event is identified by someone who has direct contact with the patient, 5) the event is considered unexpected, and 6) the reporter believes there is a causal association with the product or that causality cannot be ruled out. The suspicion that a drug is responsible for an event will usually be that of the study investigator or other clinical personnel with direct contact with the patient, although the pharmaceutical company may report on the basis of its own suspicion even if the study personnel do not infer a causal relation.

Occasionally information on suspected adverse events may be identified during the course of a study, but not as a formal part of the protocol-defined data collection. Procedures for follow-up and reporting of such information should be defined by the sponsor and research team at the time of protocol development.

Increasingly, automated databases are being used by universities, pharmaceutical companies, and other commercial enterprises to evaluate the relationship between exposure to a healthcare product and adverse events. Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines. Aggregate analysis should not be confused with the automated search for signal detection using algorithms to detect disproportionate reporting rates in data sets of spontaneous reports (data mining), which should always be considered as hypothesis generating or refinement techniques. Results obtained from these techniques should always be accompanied by the caveats regarding reporting rates and biases inherent in the collection of spontaneous reports

VII. Archiving

Secure archives must be maintained for the orderly storage and expedient retrieval of all study related material. An index shall be prepared to identify the archived contents, to identify their location, and to identify by name and location any materials that by their general nature are not retained in the study archive. Access to the archives shall be controlled and limited to authorized personnel only. Special procedures may be necessary to ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected (see, II.Protocol Development, Section I).

The archive should be maintained for at least five years after final report or first publication of study results, whichever comes later. At minimum, the study archive should contain, or refer to, the following:

A. Study protocol and all approved modifications;

B. A final report of the study

C. All source data and, where feasible, any biologic specimens. A printed sample of the master computer data file(s), if feasible, with reference to the location of the machine-readable master. All "source data" should comprise the raw data that provided the basis for the final analysis of the study. The archival material should be sufficiently detailed to permit re-editing and re-analysis;

D. Documentation adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate (see section IV(C): Study Conduct);

E. Copies of electronic versions of analytic data sets and programs, computer printouts, if feasible, including relevant execution code, which form the basis of any tables, graphs, discussions, or interpretations in the final report. Any manually developed calculations shall be documented on a work sheet and similarly retained;

F. Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits. Communication of study results to the sponsor, regulators, and scientific community should be documented;

Include, for example, questionnaires, name, make and model numbers of relevant measurement instruments, calibration information and procedures.

G. Documentation relating to the collection and processing of study data, including laboratory/research notebooks, training and reference documents for abstracts, interviews, and coders.

References

1. Chemical Manufacturers Association's Epidemiology Task Group. Guidelines for good epidemiology practices for occupational environmental epidemiologic research. JOM 1991; 33:1221-1229.

2. Austin MA, Ordovas JM, Eckfeldt JH, Tracy R, Boerwinkle E, Lalouel JM, Printz M. Guidelines of the National Heart, Lung, and Blood Institute Working Group on blood Drawing, Processing, and Storage for Genetic Studies. Am J Epidemiol 1996; 144:437-41.

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11.5 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects

must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example,

access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

sanofi pasteur MSD
vaccines for life

BUDGET GRID - EPIDEMIOLOGICAL STUDY

SC: Scientific coordinator - Dr. Carozzi

SPMSD can sub-contracts some activities

Supplier team involvement
from December 2011
to Dec 2014

Main study timelines
Protocol June 2011
Recruitment / Data collection Nov 2011 - Apr 2013
Database lock Jun 2013
Study report Dec 2013

Assumptions
nb of countries 1
countries XX Italy
nb of sites 1 - LHU Matera
nb of patients 3600 women aged 10-50

Tasks	Performed by: ISPO (SC+ team)	SPMSD	LHU team	CRO/ other	SPMSD Comments	PI Task Description (fully detailed)	Unit cost	Nb of unit	Total cost
1- Study Document preparation					[redacted]				
Protocol									già fatto nella fattibilità
Development in English		X							
review and approval		X							
translation (synopsis and/or protocol)	X		X						
translation review/validation		X		X					
Study Document review and approval									
Paper CRF development									già fatto nella fattibilità
Development in English		X							
review and approval		X							
translation	X		X						
translation review/validation		X		X					
CRF completion guidelines and updates		X							
Development in English		X							
review and approval		X							
translation	X		X						
translation review/validation				X					
study documents		X							
Questionnaire development in English		X							
Questionnaire review and approval		X							
Questionnaire translation	X	X	X						
Questionnaire translation review/validation				X					
Recruitment log development in English		X							
Recruitment log review and approval		X							
Recruitment log translation	X	X	X						
Recruitment log translation review/validation				X					
Participant log development in English		X							
Participant log review and approval		X							
Participant log translation	X	X	X						
Participant log translation review/validation				X					
study invitation letter development in English		X							
study invitation letter review and approval		X							
study invitation letter translation	X	X	X						
study invitation letter translation review/validation				X					
ICF + information letter development in English		X							
ICF + information letter review and approval		X							
ICF + information letter translation	X	X	X						
ICF + information letter review/validation				X					
2- Regulatory Requirements		X							
Health Authorities notification (if applicable)									già fatto nella fattibilità
Ethic Committee		X							
Initial file preparation									
Review		X		X					
Submission	X	X							
Revision or amendment submission			X	X					
Interim or annual reports (if applicable)				X					
Study end notification (if applicable)				X					
Data Protection France				X					
File preparation									
Submission		X							
Data Protection in Italy not applicable must be checked by the legal		X							
File preparation									
Submission		X							
3 - Recruitment /Site Selection		X							
Investigator/site selection									
Selection of the participating investigator/site									
study initiation meeting		X							5000
organisation									
preparation		X		X	invitations, booking of a meeting room, managing travel fees				6000
attending	X	X		X					
minutes	X	X	X	X	participation of all ISPO team members - cost including (preparation and attending time + follow-up activities meeting)				
study follow-up meeting		X		X					
LHU payment	X	X	X	X					
Management of contracts									
Management of invoices		X							
4 - Study Committees				X					
Experts payment									

Tasks	Performed by: ISPO (SC+ team)	SPMSD	LHU team	CRO / other	SPMSD Comments	PI Task Description (fully detailed)	Unit cost	Nb of unit		Total cost
Meetings										
Advisory Board meeting - Participation	X	X	X	X					26000	
Advisory Board meeting - Organisation		X		X						
Advisory Board meeting - Preparation	X	X		X	Can include power-point presentation - co-prepared with the SC					
Advisory Board meeting - Minutes		X		X						
Steering Committee meeting - Participation	X	X	X	X		CRO can be involved if necessary				
Steering Committee meeting - Organisation		X		X		CRO can be involved if necessary			5000	
Steering Committee meeting - Preparation	X	X		X	Can include power-point presentation - co-prepared with the SC	CRO can be involved if necessary				
Steering Committee meeting - Minutes		X		X		CRO can be involved if necessary			20000	
Face to face with SPMSD meeting - Participation	X	X	X	X		CRO can be involved if necessary				
Face to face with SPMSD meeting - Organisation		X		X		CRO can be involved if necessary				
Face to face with SPMSD meeting - Preparation	X	X		X	Can include power-point presentation	CRO can be involved if necessary				
Face to face with SPMSD meeting - Minutes		X		X		CRO can be involved if necessary				
7 - Data Management and Statistics										
Data Management activity includes all tasks listed below										110000
Data base development/set up and data dictionary					Data base structure, data entry screens for paper documents. Paper documents entered with a double dis entry process. Includes validation of the data base and the data entry screen + documentation, data entry guide preparation, data entry operators training				80000	
Import and reconciliation of LHU mirror database and ISPO laboratory results in the study database	X									
Double Data entry and data entry quality control for questionnaire	X				along study duration with regular frequency					
Simple Data entry and data entry quality control for daily report 25-60	X				include acceptable error rate					
Document tracking: questionnaire, daily report 25-60, participant form,				X	include acceptable error rate					
Data management plan development in English	X									
Data management plan validation	X				Using SPMSD template					
Programming activities (edit checks, self evident corrections etc,)		X								
Validation of checks programming	X									
Print out of queries, queries tracking, change in database due to queries, audit trail	X				tests and validation must be documented (status report on documents controls)					
Review listings	X									
Data cleaning meeting (preparation&lead)										
Final Data Base Quality Control	X				Can include power-point presentation					
Final quality control	X	X								
Database lock	X				include acceptable error rate for the quality control					
Data transfer (frozen database)	X									
Additional DB transfers	X									
Data management report in English	X									
Data management report validation	X				Using SPMSD template					
Back up and archiving of the dataset		X								
Statistics activity includes all tasks listed below	X									
Sample size calculation										
SAP development in English	X	X			[redacted]				10000	
SAP validation	X				Using SPMSD template					0
Statistic tables programming		X								600
Final analysis	X									600
Interim statistical report in English (if applicable)	X				includes programing and validation					1000
Final statistical report in English	X				The template will be developed in collaboration with SPMSD					2000
Final statistical report validation	X									
Final study report activity includes all tasks listed below		X							26000	
Development in English										2000
validation	X	X			using SPMSD template in collaboration with SPMSD					2000
Editing		X								2000
8 - Study Documents Filing and Archiving		X								
Preparation of the Study File										20000
Maintenance and archiving of study documents at the end of the study		X		X						6000
9-samples activities (include all tasks listed below)	X		X							5000
Sample management tracking form development in English/Italian					[redacted]					
sample procedure manual development in English/Italian	X									606200
Sample management form translation in English/Italian				X						
validation of translation										
sample procedure manual translation in English/Italian	X	X			[redacted]					
validation of translation				X						
Training on sample procedure for ISPO personnel and CRAs from CRO	X	X			[redacted]					
Label development	X				[redacted]					
Label printing		X		X						
Label shipment				X						
Material for sampling (for 5000 samples)				X	640 770,00 €					
Material shipment (for 5000 samples)	X									
Material re-suply	X									
Tracking of supplies shipment up to receipt including acknowledgement documentation	X						1,0			6000
Protocol analyses development	X									200
Transport of the samples from site to ISPO lab	X									1000
Sample management (Receipt/tracking/management of the sample once received,...)				X						
sample at enrollment bank (4000 samples)	X				includes control of samples and documentation at receipt					2000
DNA extraction (1500)	X						0,72	4000		36000
DNA bank 1500 (1500)	X						10,00	1400		35000
Biobanking for 5 year samples and DNA	X						0,67	1500		27000
HC2 analysis (4000)	X						10000	0		10000
HPV genotyping (1500 about ; hypothesis: 20% HPV test positive + 10% QC + 5% borderline)	X					costo strumentazione, reattivi ed esecuzione				50000
Hpv specific primer for HPV not excluded by RLB innolipa (in the case of positivi for hpv 31,33,53,58,18,66,73)	X				note* about 50% of hpv positive have to be repeat with single pcr		60	4000		240000
Cost for HPV control for all HPV types specif							100	1500		150000
validation of the HPV results	X									
QC HPV results	X									20000
results feedback to the LHU	X									
Implementation of corrections following import of HC2-HR results in the LHU mirror data base - including in "sample management"	X				regular frequency					10000
sending of HPV samples results in the study database										10000
										5000

REPERTORIO ATTI ISPO n. 62, 30/12/2010

AGREEMENT
ON THE FEASIBILITY EVALUATION CONCERNING THE EPIDEMIOLOGICAL STUDY ENTITLED "*MONITORING HPV TYPE PREVALENCE IN THE POST-VACCINATION ERA IN WOMEN LIVING IN THE BASILICATA REGION, ITALY*"
Protocol number GDS02E

ACCORDO
SULLO STUDIO DI FATTIBILITA' DELLO STUDIO EPIDEMIOLOGICO "*MONITORING HPV TYPE PREVALENCE IN THE POST-VACCINATION ERA IN WOMEN LIVING IN THE BASILICATA REGION, ITALY*"
Numero di Protocollo GDS02E

BETWEEN

The **ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA,** an organisation duly existing and organized under the laws of Italy and having its registered office at Via Cosimo il Vecchio 2, 50139 Florence, Italy, Italian Fiscal Code no. 94158910482 and VAT no. 05872050488, represented by the General Manager Dr. Gianni Amunni, born in San Giovanni Valdarno (AR), on August 6th, 1954, having his elected domicile at the above mentioned registration office of ISPO.

(Hereinafter referred to as «**ISPO**»)

AND

SANOFI PASTEUR MSD S.N.C., "Société en Nom Collectif" duly existing and organized under the laws of France, with a capital of 60.000.000 Euros, having its registered office located at 8, rue Jonas Salk, 69007 Lyon, France and registered under company number: SIREN n° 392 032 934 RCS Lyon, represented by Guy DEMOL, Vice President Development.

(Hereinafter referred to as «**SPMSD**»)

SPMSD and ISPO hereinafter also being collectively referred to as the **"Parties"** and individually referred to as the **"Party"**.

TRA

L'ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA, Istituzione costituita e vigente sotto la legge italiana, con sede legale in Via Cosimo il Vecchio, 2 – 50139 Firenze, Italia, C.F. 94158910482 e P. IVA n. 05872050488, nella persona del Direttore Generale, Dott. Gianni Amunni, nato a San Giovanni Valdarno (AR), il 6 agosto 1954, domiciliato per la carica presso la sede legale di ISPO di cui sopra.

(di seguito definita "**ISPO**")

E

SANOFI PASTEUR MSD S.N.C., Società in nome collettivo costituita ed esistente secondo la normativa francese, con un capitale sociale di € 60.000.000, sede legale in Rue Jonas Salk n. 8, 69007 Lione, Francia, registrata in Lione sotto SIREN n. 392 032 934 RCS Lione, rappresentata da Guy DEMOL, Vice PresidenteSviluppo

(di seguito definita "**SPMSD**")

SPMSD e ISPO di seguito anche definite congiuntamente **"le Parti"** o singolarmente **"la Parte"**.

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WHEREAS

SPMSD is a French leading pharmaceutical company specialized in the development, registration and distribution of vaccines for human use in the countries which composed the European Union (EU) as of May 1st, 2004 (i.e. excluding the ten acceding countries that joined the EU on May 1st, 2004) and the four countries of the European Free Trade Association.

Within the framework of its research activities, SPMSD is sponsor of an epidemiological study entitled "***Monitoring HPV type prevalence in the post-vaccination era in women living in the Basilicata region, Italy" – SIN Code GDS02E" -*** (hereinafter referred to as the "**Study**")".

SPMSD has selected ISPO that has capable personnel and the necessary accommodation to perform services as defined in Annex 1 (hereinafter referred to as the "**Services**") relating to the feasibility evaluation of the Study - (hereinafter referred to as the "**Feasability Study**")".

With ISPO's consent SPMSD has selected as scientific coordinator of the Feasibility Study Dr. Francesca CAROZZI (hereinafter referred to as the "**Scientific Coordinator**") because of her expertise in the field of Human Papilloma Virus ("**HPV**"), and the Scientific Coordinator has accepted such mission under the terms and conditions set forth hereunder.

NOW THEREFORE

In consideration of the foregoing promises and the mutual promises and the conditions herein contained, SPMSD and ISPO agree as follows on the following terms and conditions.

Art. 1 - OBJECT

Under the present agreement (hereinafter referred to

PREMESSO CHE

SPMSD, azienda francese leader nel settore farmaceutico specializzata nello sviluppo, registrazione e distribuzione di vaccini per uso umano nei paesi che costituiscono l'Unione Europea (UE) alla data del 1 maggio 2004 (ovvero ad esclusione dei 10 Paesi aderenti alla UE a partire dal 1 maggio 2004) e dei 4 Paesi che fanno parte dell'Associazione Europea per il Libero Scambio (EFTA).

Nell'ambito delle sue attività di ricerca SPMSD è lo sponsor di uno studio epidemiologico denominato ***"Monitoring HPV type prevalence in the post-vaccination era in women living in the Basilicata region, Italy" – SIN Code GDS02E"*** (di seguito definito lo "**Studio**").

SPMSD ha selezionato ISPO in quanto dispone di personale qualificato e della necessaria struttura per eseguire i servizi definiti nell'allegato 1 (di seguito definiti i "**Servizi**") relativi allo studio di fattibilità dello Studio (di seguito definito lo "**Studio di Fattibilità**")

Con il consenso di ISPO, SPMSD ha selezionato quale coordinatore scientifico dello Studio di Fattibilità la Dott.ssa Francesca CAROZZI (di seguito definito il "**Coordinatore Scientifico**"), per la sua esperienza nel campo del Papilloma Virus Umano ("HPV") ed il Coordinatore Scientifico ha accettato tale incarico nei termini ed alle condizioni riportate di seguito.

TUTTO CIÒ PREMESSO

In considerazione delle suesposte premesse e delle reciproche condizioni qui contenute, SPMSD ed ISPO si accordano sui seguenti termini e condizioni.

ART. 1 - OGGETTO

Ai sensi e per gli effetti del presente accordo (di

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as the "**Agreement**") SPMSD commits to ISPO who accepts the evaluation of the Feasibility Study in Italy and the performance of specific related Services in accordance with Annex 1.
"Agreement" means the present agreement and any and all annexes attached thereto and amendments that shall be made a part of this Agreement for all purposes and any and all other applicable terms and conditions and policies referenced in any of the preceding.

Art. 2 - ISPO's / Scientific Coordinator's OBLIGATIONS

ISPO shall perform all Services listed in Annex 1.

Art. 3 - DURATION

The present Agreement enters into in full force and effect as from its last date of signature (the "**Effective Date**") and shall terminate four (4) months by the Effective Date. It may be extended on written and express agreement between the Parties for a period of four (4) months.

None of the Parties shall be bound by any conditions, definitions, warranties, understandings or representations with respect to the present Agreement other than that as provided herein or as fully agreed in written with an amendment duly signed by the representative of the Parties.

It is understood that nothing contained in this Agreement is intended to impose on either SPMSD or ISPO any obligation to enter into a further agreement in connection with the Study.

Art. 4 - SCIENTIFIC RESPONSIBILITY

The scientific responsible designated by ISPO for the performance of the Feasibility Study is the Scientific Coordinator above mentioned.

The scientific responsible designated by SPMSD in charge of supervising all epidemiological studies is Dr Laurence SERRADELL-VALLEJO.

The Scientific Coordinator, for the performance of the Services governed by this Agreement shall be assisted by the following personnel of ISPO:

seguito l'"**Accordo**") SPMSD affida ad ISPO che accetta, la realizzazione dello Studio di Fattibilità in Italia e l'esecuzione dei Servizi specifici ed esso connessi di cui all'Allegato 1.
"Accordo" indica il presente contratto e ciascuno e tutti i relativi allegati ed emendamenti che costituiranno parte integrante e sostanziale del presente Accordo nonché tutti gli ulteriori termini e condizioni e linee guida ivi indicati.

ART. 2 - OBBLIGHI DI ISPO / DEL Coordinatore Scientifico

ISPO dovrà eseguire i Servizi indicati nell'Allegato 1.

ART. 3 - DURATA

Il presente Accordo decorrerà dalla data di apposizione dell'ultima sottoscrizione ("**Data di entrata in vigore**") ed avrà una durata di quattro (4) mesi dalla Data di entrata in vigore. La durata potrà essere estesa di ulteriori quattro (4) mesi previo accordo scritto tra le Parti.

Nessuna delle Parti sarà vincolata da nessuna condizione, definizione, garanzia, intesa o dichiarazione relativa al presente Accordo diversa rispetto a quanto disposto nel presente Accordo o da quanto espressamente concordato per iscritto tramite un apposito emendamento debitamente sottoscritto dai rappresentanti delle Parti.

Resta inteso che nulla di quanto contenuto nel presente Accordo è volto ad imporre a SPMSD o ad ISPO l'obbligo di sottoscrivere un successivo accordo in relazione allo Studio.

ART. 4 - RESPONSABILITÀ SCIENTIFICA

Il responsabile scientifico designato da ISPO per l'esecuzione dello Studio di Fattibilità è il Coordinatore Scientifico sopra menzionato.

Il responsabile scientifico designato da SPMSD incaricato di supervisionare tutti gli studi epidemiologici è il Dott.ssa Laurence SERRADELL-VALLEJO.

Il Coordinatore Scientifico, per l'esecuzione dei Servizi oggetto del presente Accordo sarà assistito

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- Dr. Massimo Confortini (for the activities regarding the citology);
- Dr. Marco Zappa and Dr. Donella Puliti (for the evaluation, data entry and management, flows organization);
- Dr. Paola Mantellini (for the recruiting in the Basilicata Region, forms and ethic committee)
- Dr. Simonetta Bisanzi (HPV test operations and relevant procedures).

ISPO in person of the Scientific Coordinator of the Feasibility Study is entitled to modify, supplement, substitute ISPO's personnel who participate to the said Feasibility Study, it being understood that ISPO shall guarantee the presence of the required skills and competences for the performance of the different activities object of this Agreement. Any modification of the personnel shall be communicated in advance through e-mail addressed to Dr. Laurence SERRADELL.

Art. 5 - FINANCIAL PROVISIONS

For the Services rendered under this Agreement, as detailed in Annex 1, SPMSD undertakes to pay ISPO the total amount of € 114.800 (one hundred fourteen thousand and eight hundred EUR), VAT excluded if due (hereinafter referred to as the "**Budget**").

The mentioned sum shall not be modified and is considered as comprehensive of any expenses, direct or indirect, already met and/or to meet for the performance of the Services object of this Agreement It is understood between the Parties that pass-through expenses including but not limited to travel, meetings, transportation, accommodation, catering expenses incurred within the framework of the Feasibility Study and accessory to the said Services are included in the Budget.

SPMSD shall pay to ISPO the mentioned amount through bank transfer (on the bank account no. 8C01, IBAN IT53L0616002832000000008C01 - Banca CR Firenze SpA, Filiale Enti e Tesorerie, via del Castellaccio n. 36/38 – 50121 Firenze) as follows:

1) 50 % at the signature of this Agreement;

dal seguente personale di ISPO:
- Dott.. Massimo Confortini (per le attività relative alla citologia);
- Dott.. Marco Zappa e la Dott..ssa Donella Puliti (per la parte valutativa, registrazione dati, data management, organizzazione flussi);
- Dott..ssa Paola Mantellini (per il reclutamento in Basilicata, modulistica e comitato etico)
- Dott.ssa Simonetta Bisanzi (operatività test HPV e relative procedure).

ISPO nella persona del Coordinatore Scientifico per lo Studio di Fattibilità ha la piena facoltà di modificare, integrare, sostituire il personale di ISPO che partecipa a tale Studio di Fattibilità, fermo restando l'obbligo di ISPO di garantire la presenza delle professionalità e competenze necessarie alla conduzione delle diverse attività oggetto del presente Accordo. Ogni modifica del personale sarà preventivamente comunicata per e-mail indirizzata al Dott.ssa Laurence SERRADELL.

ART. 5 - CORRISPETTIVO E PAGAMENTO

Per i Servizi oggetto del presente Accordo, in indicati dettagliatamente nell'Allegato 1, SPMSD si impegna a corrispondere ad ISPO la somma complessiva di € 114.800,00 (cento quattordicimila ottocento euro/00), IVA esclusa se dovuta (di seguito definito il "**Budget**").

La somma sopra indicata, non è soggetta a variazione e si intende comprensiva di ogni spesa diretta ed indiretta sostenuta e/o da sostenere per l'espletamento dei Servizi oggetto del presente Accordo. Resta inteso tra le Parti che le spese di trasferta, comprensive di ma non limitate a, viaggi, meeting, trasporti, alloggio, catering sostenuti nell'ambito dello Studio di Fattibilità ed inerenti ai predetti Servizi sono inclusi nel Budget.

SMPSD verserà ad ISPO la predetta somma a mezzo bonifico bancario su conto corrente intestato ad ISPO (Conto Corrente n. 8C01, IBAN IT53L0616002832000000008C01 Banca CR Firenze SpA, Filiale Enti e Tesorerie, via del Castellaccio n. 36/38 – 50121 Firenze)
secondo le seguenti modalità:

1) il 50 % alla sottoscrizione del presente Accordo;

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2) 50% at the conclusion of the Feasibility Study evaluation, by prior delivery by ISPO of the final version of the Report as per Annex 1.

Prior to each payment, ISPO shall establish an invoice to the name of Dr. Laurence SERRADELL Sanofi Pasteur MSD S.N.C. - 8, rue Jonas Salk, 69367 LYON Cedex 07 France.

Each invoice shall be established exclusive taxes and shall mention the following elements:

- the reference of the Study : GDS02E
- the detail of the Services performed by ISPO
- the corresponding fees owed to ISPO
- SPMSD intra-European VAT number: FR04 392 032 934
- ISPO intra-European VAT number: IT 05872050488
- Any additional special national features if applicable

The payment of the invoices shall be made within 60 (sixty) days end of month following invoice date receipt.

Art. 6 - MEETING AND MATERIAL FOR THE PERFORMANCE OF THE EVALUATION

SMPSD undertakes to organize and coordinate the meetings between ISPO – through its Scientific Coordinator or the persons delegated by the latter – and the centers of the Basilicata Region involved and to supply all the information needed by ISPO and the Scientific Coordinator to perform the Feasibility Study including but not limited to the Local Health Unit of Matera obligations regarding the Study.

SMPSD guarantees the presence of its own personnel at the meeting to be held in Florence, Italy at ISPO premises, and at the visits on site in Basilicata.

Art. 7 - WITHDRAWAL

The Parties may withdraw from this Agreement at any time by giving a prior written notice of at least thirty (30) days through registered mail with advice

2) il 50% alla conclusione della realizzazione dello Studio di Fattibilità, previa consegna da parte di ISPO della versione finale della Relazione scritta di cui all'Allegato 1.

Prima di ciascun pagamento, ISPO dovrà emettere una fattura intestata a Dott.ssa Laurence SERRADELL Sanofi Pasteur MSD S.N.C. - 8, rue Jonas Salk, 69367 LYON Cedex 07 Francia.

Ciascuna fattura dovrà essere emessa tasse escluse e dovrà contenere i seguenti elementi:

- il riferimento dello Studio: GDS02E
- il dettaglio dei Servizi eseguiti da ISPO
- l'importo dei corrispettivi dovuti ad ISPO
- la Partita IVA intra-europea di SPMSD: FR04 392 032 934
- la Partita IVA intra-europea di ISPO: IT 05872050488
- ogni ulteriore elemento richiesto dalla normativa nazionale, se applicabile

Il pagamento delle fatture sarà effettuato entro 60 (sessanta) giorni fine mese data ricevimento fattura.

ART. 6 - MEETING E MATERIALE PER L'ESECUZIONE DELLA VALUTAZIONE

SMPSD si impegna ad organizzare e coordinare gli incontri tra ISPO - per il tramite del Coordinatore Scientifico o delle persone da esso delegate - ed i centri della Basilicata coinvolti ed a fornire tutta la documentazione di cui necessita ISPO ed il Coordinatore Scientifico per eseguire lo Studio di Fattibilità ivi compresi, ma non limitatamente a, gli obblighi dell'Azienda Sanitaria Locale di Matera relativamente allo Studio.

SMPSD garantisce la presenza di proprio personale durante le riunioni che si terranno a Firenze, Italia presso ISPO, ed in occasione delle visite on site in Basilicata.

ART. 7 - RECESSO

Le Parti potranno recedere dal presente Accordo in ogni tempo, con un preavviso scritto di almeno 30 giorni a mezzo raccomandata A/R; in tal caso sono

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of receipt; in said event, without prejudice to the expenses already incurred or the undertakings in force at the date of the withdrawal's communication.

Art. 8 - CONFIDENTIALITY AND PRIVACY

ISPO takes note and acknowledges the important strategic value of any data, information, and/or document relating to the Feasibility Study and regarding SPMSD of which it has become acquainted with in any way before, during and after the performance of the Services under this Agreement, and therefore undertakes expressly to keep confidential and not to misuse or disclose to third parties the said data, documents and/or information, for the entire duration of this Agreement and also after its expiration for a period of ten (10) years.

ISPO undertakes to extend the said confidentiality obligation also to its employees and/or collaborators including the Scientific Coordinator.

ISPO guarantees that all the participants to the Feasibility Study undertake to keep confidential any information, data and/or document of which they have become acquainted with, or of which they came into possession and which are directly connected to and/or deriving from the Services object of this Agreement.

Art. 9 - REFERENCES PROVISIONS

For anything that has not been expressly regulated by this Agreement, the relevant provisions of Italian laws shall be applied.

Art. 10 - REGISTRATION EXPENSES

This Agreement shall be registered in case of use according to Articles 5, 6, 39 and 40 of Presidential Decree no. 131 dated April 26, 1986 by the Party who is interested to do so. The stamp duties shall be charged on each Party according to the amount of competence.

fatte salve le spese già sostenute o gli impegni assunti, alla data di comunicazione del recesso.

ART. 8 - RISERVATEZZA E PRIVACY

ISPO prende atto e riconosce l'importante valore strategico di ogni dato, documento e/o informazione riguardante lo Studio di Fattibilità e relativo a SPMSD di cui sia venuto a conoscenza in qualsiasi modo prima, durante e dopo l'esecuzione dei Servizi oggetto del presente Accordo e pertanto si impegna espressamente a mantenere riservati e non fare uso improprio o a divulgare a terzi i suddetti dati, documenti e/o informazioni, per l'intera durata del presente Accordo ed anche dopo la sua scadenza per un periodo di dieci (10) anni.

ISPO si impegna ad estendere tale vincolo di riservatezza ai propri dipendenti e/o collaboratori incluso il Coordinatore Scientifico.

ISPO assicura che tutti i partecipanti allo Studio di Fattibilità si impegnano a mantenere la riservatezza sui dati, documenti e/o informazioni dei quali abbiano conoscenza, possesso e detenzione, direttamente connessi e/o derivanti dai Servizi oggetto del presente Accordo.

ART. 9 - NORME DI RINVIO

Per quanto non espressamente previsto nel presente Accordo, si applicano le norme di diritto italiano vigenti in materia.

ART. 10 - SPESE DI REGISTRAZIONE

Il presente atto è soggetto a registrazione in caso d'uso ai sensi degli art. 5, 6, 39 e 40 del D.P.R. n° 131 del 26/04/1986 a cura ed onere della parte che ha interesse a farlo. Le spese di bollo sono a carico di ciascuna delle Parti secondo quanto di competenza.

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Art. 11 - LITIGATION / PLACE OF JURIDISCTION

Any disputes, misunderstanding and/or differences arising out of or in connection with this Agreement are settled amicably by the Parties.

If however such settlement cannot be reached on an amicable basis, using good faith efforts and within a period of sixty (60) days, such disputes, misunderstanding and/or differences is definitively settled by the competent Courts of Florence, Italy.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be duly executed as of the Effective Date.

For ISPO

Dr. Dott.. Gianni Amunni
General Manager

Date: 30 DIC. 2010
Place: FIRENZE
Signature:

For SPMSD

Guy DEMOL
Vice President Development

Date: 21/12/10
Place: Lyon
Signature:

ART. 11 - CONTROVERSIE/GIURISDIZIONE

Tutte le controversie, malintesi e/o contestazioni derivanti da o in relazione al presente Accordo saranno definiti in modo amichevole tra le Parti.

Se, tuttavia, tale composizione amichevole non potesse essere raggiunta, usando buona fede, entro il termine di sessanta (60) giorni, tali controversie, malintesi e/o contestazioni saranno definitivamente devolute alla competenza del Tribunale di Firenze, Italia.

IN CONSIDERAZIONE DI TUTTO QUANTO SOPRA DISPOSTO, le Parti hanno stabilito che il presente Accordo venga puntualmente eseguito a far data dalla sua sottoscrizione.

Per ISPO

Dott.. Gianni Amunni
Il Direttore Generale

Data: 30 DIC. 2010
Luogo: FIRENZE
Firma:

Per SPMSD

Guy DEMOL
Vice Presidente Sviluppo

Data: 21/12/10
Luogo: Lyon
Firma:

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Annex 1 : ISPO's Activities

Evaluation of the project, feasibility and logistics of the Study:

- Analysis, evaluation and validation of the Study protocol and of the sample size
- Support for the determination of organization methods regarding the recruitment to the study
  - Evaluation of the procedures and/or organization of the recruitment to the study of women aged 25-50 years and for young women aged 18-24 years
  - Definition of draft procedures regarding the phase of collection of biological samples for HPV
  - Definition of draft procedures regarding the transmission methods of the samples to ISPO's laboratory
  - Definition of draft procedures regarding the cytology quality control
  - Definition of draft procedures regarding the transmission of HPV results with Hc2 method from ISPO's laboratory to the screening center of Basilicata.
- Investigation of the data management and the statistical analysis feasibility
  - Definition and sharing of the specifications of the relevant database of the Study for the data management
  - Evaluation of the current databases (cervical screening, vaccination data, HPV results, questionnaire data, CRF data and recruitment log data) and their compatibility with the Study feasibility
  - Evaluation of the registration methods of the recruitment data
  - Evaluation and definition of the data extraction methods for matching vaccine registry and screening registry for transmission to ISPO on a monthly basis
  - Feasibility of a quality control of the extraction prior to the transmission
- The results of this feasibility step will be compiled in a feasibility report.
- Review and approval of the following:
  - Questionnaire to submit to the women at their recruitment (Italian and English

Allegato 1: Attività di ISPO

Valutazione della progettazione, fattibilità e logistica dello Studio:

- Analisi, valutazione e validazione del protocollo dello Studio e della dimensione del campione
- Supporto per la determinazione delle modalità organizzative per l'arruolamento nello studio
  - Valutazione delle procedure e/o organizzazione dell'arruolamento nello studio delle donne di 25-50 anni e per le ragazze di 18-24 anni
  - Definizione delle bozze di procedure relative alla fase di raccolta campioni biologici per HPV
  - Definizione delle bozze di procedure relative alle modalità di invio dei campioni al laboratorio di ISPO
  - Definizione delle bozze di procedure relative al controllo di qualità citologia
  - Definizione delle bozze di procedure riguardanti l'invio dei risultati HPV con metodica Hc2 dal laboratorio ISPO al centro screening della Basilicata:
- Analisi del data management e indagine della fattibilità dell'analisi statistica
  - Definizione e condivisione delle specificità del data base relativo allo Studio per il data management
  - Valutazione dei database attuali (cervical screening, vaccination data, HPV results, questionnaire data, CRF data and recruitment log data) e loro compatibilità con la fattibilità dello Studio
  - Valutazione delle modalità di registrazione dei dati di arruolamento
  - Valutazione e definizione delle modalità di estrazione dei dati per incrocio registri vaccinali e di screening per invio ad ISPO su base mensile
  - Fattibilità di un controllo di qualità dell'estrazione prima dell'invio
- I risultati di tale step di fattibilità saranno riportati in una relazione sulla fattibilità
- Revisione ed approvazione dei seguenti:
  - questionario da sottoporre alle donne

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version)

- Invitation letter (Italian and English version)
- Material for the Ethic Committee (forms and informed consent, Italian and English version

- Support in the French data protection document completion.

The present project for the evaluation of the feasibility of the Study provides a meeting in Florence with SPMSD and one or two (2) visit(s) in Basilicata in order to verify all of the above mentioned issues.

all'arruolamento (versione inglese e versione italiana)

- Lettera di invito (versione inglese e versione italiana)
- Materiale per il comitato etico (modulistica e consenso informato, versione inglese e versione italiana)

- Assistenza alla compilazione del documento francese relativo alla protezione dei dati personali.

Il presente progetto per la valutazione della fattibilità dello Studio prevede una riunione a Firenze con SMPSD e una o due (2) visite in Basilicata per verificare tutti i punti sopra-menzionati.

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