Regione Toscana
Direzione Sanità, Welfare e Coesione Sociale
Settore Ricerca e investimenti in ambito sanitario
BANDO RICERCA SALUTE 2018
Bando pubblico regionale per progetti di ricerca e sviluppo mirati al sostegno ai processi di innovazione clinica e organizzativa del Servizio Sanitario Regionale

CONVENZIONE PER LA REALIZZAZIONE DEL PROGETTO "Tuscany project to investigate on efficacy and safety of Cannabis phytotherapic preparations for the treatment of Aromatase iNhibitor-induced chronic resistaNt pAin in Breast cancer patIents: a prospective multicenter randomized placebo-controlled phase III Study - TosCANNABIS"

TRA

REGIONE TOSCANA

E

AZIENDA OSPEDALIERO UNIVERSITARIA CAREGGI

La REGIONE TOSCANA con sede in Firenze, Palazzo Strozzi Sacrati, Piazza del Duomo n. 10, C.F. e P. IVA n. 01386030488, rappresentata dal Dirigente regionale Elisa Nannicini nata a Firenze il 05/10/1971, domiciliata presso la sede dell'Ente, la quale interviene nella sua qualità di Dirigente del Settore "Ricerca e investimenti in ambito sanitario", struttura competente per materia, nominata con decreto n. 8677 del 21/5/2021 ed autorizzata, ai sensi dell'art. 54 della L. R. 13/07/07 n. 38, ad impegnare legalmente e formalmente l'Ente medesimo con il presente atto, il cui schema è stato approvato con D.D n. 975 del 16/01/2020;

E

L'ente Azienda Ospedaliero Universitaria Careggi, (di seguito denominato "Capofila"), con sede legale in Firenze, Largo Brambilla, n.3 – C.F./P.I. 04612750481, rappresentato dal Sig. Rocco Donato Damone, nato a Tolve (PZ) il 29/02/1956, in qualità di legale rappresentante pro tempore, domiciliato per il presente atto presso la sede dell'ente o da persona eventualmente da egli delegata per giusta procura che si allega al presente Contratto, Soggetto Capofila e mandatario del raggruppamento ATS costituito a Firenze, in data 09/06/2020 con atto del Notaio Rosanna Montano (repertorio n.62807, fascicolo n.18694), registrato a Firenze il 10/06/2020, al n. 19204 Serie 1T tra i seguenti soggetti:

1. Azienda Ospedaliero Universitaria Careggi - Largo Brambilla, n.3 – Firenze;
2. Università degli Studi di Firenze - Piazza S. Marco, 4 – 50121 Firenze;
3. Istituto per lo studio, la prevenzione e la rete oncologica ISPRO - Via Cosimo il Vecchio, n. 2 – Firenze;
4. Azienda USL Toscana Centro - Piazza Santa Maria Nuova, 1 – Firenze

PREMESSO CHE

- in data 10 ottobre 2018 sul SUPP n.170 al B.U.R.T, pIII, è stato pubblicato il Decreto Dirigenziale n. 15397 del 26 settembre 2018, di approvazione del "Bando Ricerca Salute 2018 - Bando pubblico regionale per progetti di ricerca e sviluppo mirati al sostegno ai processi di innovazione clinica e organizzativa del Servizio Sanitario Regionale";

- con il D.D n. 16906 del 15/10/2019 sono stati approvati gli esiti della valutazione e con il DD n. 975 del 16/01/2020 e si è provveduto alla identificazione dei progetti ammessi a finanziamento sulla base della disponibilità di fondi;
- il Progetto denominato "Tuscany project to investigate on efficacy and safety of Cannabis phytotherapic preparations for the treatment of Aromatase iNhibitor-induced chronic resistaNt pAin in Breast cancer patIents: a prospective multicenter randomized placebo-controlled phase III Study - TosCANNABIS", numero CUP D18D20001310002, (d'ora in avanti denominato "Progetto"), risulta tra gli ammessi a contributo sulla base della disponibilità di fondi, come risulta dal citato decreto n. 975 del 16/01/2020;
- l'ammissione a contributo è condizionata alla verifica con esito positivo nonché al mantenimento dei requisiti previsti e dichiarati in sede di presentazione della domanda di partecipazione e ad ogni altra condizione necessaria prevista dalla normativa vigente e dal Bando;

VISTA

la normativa di riferimento ed, in particolare:

- la legge regionale n. 40 del 24 febbraio 2005 e s.m.,
- il Programma regionale di sviluppo 2016-2020 approvato dal Consiglio regionale con la risoluzione n. 47 del 15 marzo 2017;
- la deliberazione del Consiglio Regionale n. 54 del 31 luglio 2019 "Approvazione del Documento di Economia e Finanza Regionale (DEFR) 2020";
- il "Piano Sanitario e Sociale Integrato Regionale 2018-2020" approvato con Deliberazione del Consiglio Regionale n. 73 del 09/10/2019;
- la "Strategia di Ricerca e Innovazione per la Smart Specialisation in Toscana" (DGR 1018/2014);
- la decisione G.R. n. 4 del 7 aprile 2014;
- la Delibera della Giunta Regionale n. 672 del 18 giugno 2018;
- il Decreto n. 15397 del 26 settembre 2018;
- la Delibera 648 del 13 maggio 2019;
- il Decreto 16906 del 15 ottobre 2019

TUTTO CIÒ PREMESSO

i contraenti, come sopra costituiti, convengono e stipulano quanto segue:

Art. 1 – Oggetto

La presente Convenzione ha per oggetto la realizzazione del Progetto "Tuscany project to investigate on efficacy and safety of Cannabis phytotherapic preparations for the treatment of Aromatase iNhibitor-induced chronic resistaNt pAin in Breast cancer patIents: a prospective multicenter randomized placebo-controlled phase III Study - TosCANNABIS".

Art. 2 – Durata

La presente Convenzione - sottoscritta ai sensi dell'art. 15 della L. n. 241/1990 e ss.mm.ii. - ha decorrenza dalla data di apposizione dell'ultima firma e della marca temporale della stessa e ha validità fino ai cinque anni successivi alla rendicontazione del progetto realizzato.
La data dell'ultima firma e della marca temporale apposta sulla convenzione costituisce la data di

avvio del progetto.
Il progetto deve essere completato entro 36 mesi dalla data di avvio del progetto.
La Regione, in accordo con l'art. 6.3 del Bando, può concedere una sola proroga delle attività del Progetto per un periodo massimo di 6 mesi, previa istanza del Capofila da presentarsi entro 60 giorni dalla data prevista di conclusione del Progetto.
La richiesta di proroga deve essere motivata e corredata da una relazione sullo stato di avanzamento del progetto e della spesa.

Art. 3 – Obblighi della Regione Toscana

La Regione Toscana si impegna a corrispondere al Capofila, nelle forme e modalità stabilite dalla presente Convenzione, un contributo fino ad un massimo di euro 279.000 (*duecentosettantanovemila)* a fronte di un costo totale del progetto pari ad euro 350.000 *(trecentocinquantamila)* nella forma del contributo a fondo perduto.
Il contributo è concesso con le seguenti modalità:

1. in anticipazione (facoltativa) fino al 40% del totale del contributo, previa presentazione di garanzia fideiussoria (tale garanzia non è richiesta nel caso di OR pubblici e di enti del Servizio Sanitario) da parte di ciascun componente dell'ATS di cui il Capofila è mandatario; la domanda di anticipo deve essere presentata direttamente a Regione Toscana entro 1 mese dalla data di sottoscrizione della presente convenzione;
2. per stato avanzamento lavori (d'ora in avanti "SAL") – (obbligatoria), pari al 30% (proporzionalmente alle spese ammissibili rendicontate), da presentare entro 30 giorni dalla data di conclusione del primo periodo di rendicontazione (18 mesi dalla data di avvio del progetto).
   La domanda a titolo di SAL deve essere presentata dal Capofila a Regione Toscana unitamente alla rendicontazione dei costi totali sostenuti e si compone di:
   - relazione tecnica intermedia sullo stato di avanzamento del progetto, elaborata in base allo schema fornito dalla Regione Toscana;
   - fatture o documenti contabili di equivalente valore probatorio, completi di documentazione relativa al pagamento, rappresentata dalla ricevuta contabile del bonifico o altro documento (bancario) relativo allo strumento di pagamento prescelto, in cui sia documentato il sottostante movimento finanziario, con indicazione nella causale degli estremi del titolo di spesa a cui il pagamento si riferisce (normativa antiriciclaggio D.Lgs. 231/07).

   La mancata rendicontazione delle spese per almeno 30% del costo totale del progetto e/o la mancata presentazione della relazione tecnica intermedia sarà considerata come rinuncia implicita dei beneficiari alla realizzazione del progetto e, trascorsi ulteriori 30 giorni dalla scadenza dei termini, determinerà la revoca dell'intero contributo secondo le modalità e i termini stabiliti all'art. 17 del Bando.
   La quota del SAL sarà erogato solo nel caso in cui sia il controllo sulla rendicontazione presentata che la valutazione sulla relazione intermedia sullo stato di avanzamento del progetto abbiano avuto esito positivo.
3. a saldo, pari alla quota restante di contributo; l'esatto ammontare del contributo da erogare verrà determinato sulla base delle spese ritenute ammissibili di cui all'art. 8 del Bando e alle "Linee guida per la rendicontazione" approvate con D.D. n. 17367 del 6/11/18.
   La richiesta di pagamento saldo deve essere presentata dal Capofila, entro 30 giorni dalla conclusione del secondo periodo di rendicontazione (36 mesi dalla data di avvio del progetto o entro nuovo termine concesso dall'Amministrazione a seguito di proroga), unitamente alla relazione tecnica conclusiva.

Il saldo sarà erogato solo nel caso in cui sia il controllo sulla rendicontazione presentata che la valutazione sulla relazione finale del progetto abbiano avuto esito positivo.

L'erogazione del contributo è subordinata alla verifica del mantenimento da parte del Capofila e di ciascun componente dell'ATS dei requisiti per l'accesso al contributo di cui all'art. 5 del Bando.

Art. 4 – Obblighi del Capofila e di ciascun componente dell'ATS

Nel rispetto degli obblighi della normativa di riferimento, del Bando di cui alle premesse e della presente Convenzione, il Capofila e ciascun componente dell'ATS si impegnano a:

1. realizzare il progetto entro il termine indicato nella proposta progettuale, conformemente all'oggetto, agli obiettivi e ai risultati attesi della ricerca contenuti nel progetto approvato, ferme restando le eccezioni previste all'art. 16 del Bando;
2. comunicare, anticipatamente e tempestivamente, tutte le modifiche inerenti al progetto approvato;
3. rendicontare le spese effettivamente sostenute per la realizzazione del progetto come definito nell'art. 12 del Bando fornendo le relazioni tecniche per ciascun stato di avanzamento, al diciottesimo ed al trentaseiesimo mese dalla data di avvio progetto;
4. garantire la conservazione fino al quinto anno successivo all'erogazione del saldo della documentazione scientifica e contabile inerente la sua realizzazione;
5. consentire ai funzionari della Regione Toscana o a soggetti da essa incaricati, lo svolgimento di controlli o ispezioni;
6. rispettare gli obblighi di informazione e pubblicità previsti dall'art. 11 del bando.
   Ciascun partner di progetto autorizza la Regione Toscana a pubblicare, anche per estratto, le relazioni intermedia e finale del progetto di ricerca e le relative valutazioni, nel rispetto della tutela dei dati personali e nel rispetto della tutela dei diritti di proprietà intellettuale inerenti ai risultati del progetto.
7. rispettare il divieto di cumulo impegnandosi per il futuro a non cumulare altri finanziamenti per le stesse attività progettuali;
8. mantenere i requisiti di ammissibilità di cui all'art. 5 del Bando per tutta la durata del progetto e comunque fino all'istanza di erogazione del saldo;
9. comunicare tempestivamente al Responsabile del procedimento, mediante PEC all'indirizzo regionetoscana@postacert.toscana.it l'eventuale rinuncia al contributo.

Art. 5 – Obblighi del Capofila

Il Capofila opera in qualità di mandatario dell'ATS ammessa a finanziamento con il Progetto e, in quanto tale ha l'obbligo di:

1)assicurare il buon funzionamento e il raggiungimento degli obiettivi progettuali,

2)curare la conservazione di tutti gli elaborati tecnici, della documentazione amministrativa e contabile del progetto, separata o separabile mediante opportuna codifica dagli altri atti amministrativi generali; detta archiviazione deve essere accessibile senza limitazioni, ai fini di controllo, alle persone ed agli organismi aventi diritto e deve essere conservata per almeno cinque anni successivi all'erogazione del saldo del contributo;

3) fornire le informazioni e le documentazioni finanziarie, tecniche e amministrative del Progetto e dei partner dell'ATS richieste dalla Regione.

4) incassare le quote di contributo spettanti a ciascun partner e provvedere a liquidare, entro un massimo di trenta giorni, il contributo di competenza di ciascun partner di progetto, dando dimostrazione alla Regione Toscana dell'effettiva liquidazione ed esonerando la Regione da qualsiasi responsabilità per i pagamenti ad esso effettuati.

Art. 6 - Spese ammissibili e rendicontazione

Le spese ammissibili sono quelle indicate all'art. 8 del bando purché effettivamente sostenute dai beneficiari tra la data di avvio del progetto di cui all'articolo 2 della presente Convenzione ed i 36 mesi successivi, salvo proroga concessa ai sensi dell'articolo 2 della presente Convenzione ed all'art. 6.3 del Bando.
La rendicontazione delle spese sostenute deve essere presentata secondo le modalità stabilite negli articoli 12 e 13 del Bando e nelle "Linee guida per la rendicontazione".

Art. 7 - Erogazione del contributo

L'erogazione del contributo è effettuata al Capofila di progetto secondo le modalità indicate all'articolo 12 del Bando e nelle Linee guida per la rendicontazione.

Art. 8 - Divieto di cumulo

Il contributo di cui al Bando ed alla presente Convenzione non è cumulabile con altri finanziamenti, contributi o incentivi pubblici concessi per le stesse iniziative ed aventi ad oggetto le stesse spese.

Art. 9 - Valutazione intermedia e finale

Il Progetto, oltre alla valutazione preliminare per accedere al finanziamento, è sottoposto a valutazione intermedia e finale dei risultati conseguiti.
La valutazione intermedia e finale verrà effettuata da valutatori individuati secondo i criteri e le modalità riportate nell'art. 13 del Bando.
Le suddette valutazioni sono effettuate sulla base delle informazioni fornite nelle relazioni tecniche intermedie e finali, allegate alle relative rendicontazioni, come specificato all'articolo 13 del Bando, e sono dirette ad accertare:

- la coerenza dell'oggetto, degli obiettivi e dei risultati conseguiti dal progetto realizzato rispetto a quello ammesso a finanziamento;
- per la sola valutazione intermedia, la potenzialità del progetto di perseguire gli obiettivi dichiarati in fase di presentazione della domanda che non sono stati ancora raggiunti;
- la congruità delle spese sostenute, il rispetto del cronoprogramma e degli altri elementi di progetto approvato.

Le relazioni tecniche intermedie e finali devono essere elaborate conformemente alle indicazioni fornite dall'Amministrazione regionale.
Le relazioni tecniche dovranno essere trasmesse - entro 30 giorni dalla scadenza rispettivamente del diciottesimo e del trentaseiesimo mese dall'inizio del progetto (o entro nuovo termine concesso dall'Amministrazione a seguito di proroga) - all'indirizzo pec regionetoscana@postacert.toscana.it e contestualmente caricate in upload sul Sistema Unificato di Monitoraggio dei progetti in Toscana" (MoniToscana) all'indirizzo https://web.rete.toscana.it/monitoscana.
Eventuali difformità, fra risultati attesi e risultati conseguiti, dovranno essere adeguatamente motivate.
Il Capofila dovrà fornire tutte le informazioni e le documentazioni finanziarie, tecniche e amministrative del Progetto richieste dalla Regione; dovrà inoltre fornire le attestazioni necessarie per la verifica del possesso e del mantenimento dei requisiti di cui al Bando ed eventuali integrazioni, entro un termine massimo di 10 giorni dalla richiesta, se non diversamente stabilito.
La mancata trasmissione delle relazioni intermedia e finale sullo stato di attuazione del progetto, la mancata motivazione di eventuali difformità rispetto al progetto approvato o la mancata rispondenza delle relazioni a quanto indicato nel bando comportano la sospensione delle erogazioni e l'eventuale revoca del contributo.
La Regione Toscana si riserva il diritto di richiedere, in qualsiasi momento, al Capofila una

relazione relativa allo stato di avanzamento del progetto e di organizzare incontri con il gruppo di ricerca.

Art. 10 - Proprietà intellettuale e diffusione dei risultati

I risultati, le invenzioni, il knowhow, gli eventuali dati o informazioni, compresi gli eventuali software realizzati ad hoc per la ricerca, brevettabili o meno, ed ogni altro diritto di proprietà intellettuale raggiunti o realizzati nel corso dell'attività di ricerca inerente al progetto (foreground, knowledge), appartengono congiuntamente ai soggetti beneficiari del progetto ed agli eventuali enti partecipanti, ai sensi dell'art. 4 del bando, in misura proporzionale al relativo contributo inventivo; i beneficiari e gli eventuali enti partecipanti coinvolti concluderanno un accordo atto a definire l'effettiva ripartizione e le condizioni di esercizio di tale comproprietà.

I diritti di proprietà intellettuale già sviluppati, al momento della stipula della convenzione (inizio del progetto), dai soggetti beneficiari e dagli eventuali enti partecipanti coinvolti nell'attività di ricerca (background, pre-existing know-how) rimangono di loro propria titolarità.

Ogni soggetto beneficiario e l'eventuale organismo partecipante ai sensi dell'art. 4 del bando, hanno il diritto di pubblicare i risultati del progetto di ricerca nella misura in cui derivino da ricerche da essi svolte, fermo restando l'obbligo di riservatezza nel trattamento dei risultati acquisiti, necessario per l'espletamento dell'attività relativa all'utilizzo ed allo sfruttamento degli stessi, ivi compreso l'eventuale deposito di titoli di proprietà intellettuale ad essi correlati.

Le pubblicazioni e ogni altro mezzo di divulgazione dei risultati derivanti dal progetto, dovranno riportare la seguente dicitura: "Il presente progetto di ricerca è stato realizzato grazie al contributo della Regione Toscana"- "This research project is funded by Tuscany Region".

Ciascun partner di progetto autorizza la Regione Toscana a pubblicare, anche per estratto, le relazioni intermedie e finali del progetto di ricerca e le relative valutazioni, nel rispetto della tutela dei dati personali e nel rispetto della tutela dei diritti di proprietà intellettuale inerenti ai risultati del progetto.

Per ogni altro riferimento in merito a diritti di proprietà intellettuale e diffusione dei risultati, si rimanda a quanto previsto dallo specifico accordo, sottoscritto ed allegato alla presente Convenzione in copia conforme all'originale (Allegato 3).

Art. 11 - Ispezioni e controlli

La Regione Toscana si riserva di effettuare, in qualsiasi momento, ispezioni documentali presso i soggetti beneficiari allo scopo di verificare lo stato di esecuzione, il rispetto degli obblighi previsti dalla normativa vigente e dal bando e la veridicità delle informazioni fornite dai soggetti beneficiari stessi.

L'Amministrazione regionale procederà a controlli effettuati su tutti i soggetti finanziati ed a controlli a campione secondo le modalità stabilite all'articolo 15 del Bando.

Art. 12 - Sospensione delle erogazioni e revoche

È disposta la sospensione del contributo qualora emerga la mancata o ritardata attuazione del progetto e delle relative spese e l'inottemperanza agli obblighi di cui all'art. 4 della presente convenzione.

Il contributo sarà revocato nei seguenti casi:

a) rinuncia del soggetto beneficiario;
b) mancato rispetto degli obblighi di cui all'art. 4 della presente convenzione; per gli obblighi di cui all'art. 4 punto 2, la Regione Toscana si riserva, prima di procedere a revoca, una valutazione a proprio insindacabile giudizio della rilevanza del mancato rispetto;

c) inadempienze dei soggetti beneficiari rispetto ai requisiti soggettivi ed oggettivi di cui agli art. 3, 5 e 6 del bando, nonché tutte le altre violazioni della normativa di riferimento;
d) mancata attuazione degli adempimenti successivi all'ammissione a finanziamento;
e) esito negativo dei controlli svolti nei 180 giorni successivi alla pubblicazione sul BURT del decreto di approvazione della graduatoria.

La Regione Toscana, qualora si verifichino le circostanze che danno luogo alla revoca del contributo, comunica agli interessati l'avvio del procedimento con indicazioni relative all'oggetto del procedimento promosso, all'ufficio e alla persona responsabile del procedimento, presso i quali si può prendere visione degli atti, e assegna ai destinatari un termine di 30 giorni, decorrente dalla ricezione della comunicazione stessa, per presentare eventuali controdeduzioni o scritti difensivi, redatti in carta libera, nonché altra documentazione ritenuta idonea. La presentazione degli scritti e della documentazione di cui sopra deve avvenire con la stessa modalità utilizzata dalla Regione Toscana per la notifica dell'avvio del procedimento.
I contributi indebitamente percepiti dovranno essere restituiti dai soggetti beneficiari interessati.

Art. 13 - Difforme e/o parziale realizzazione del progetto

Costituiscono difforme e/o parziale realizzazione del progetto la:
1. non completa/parziale realizzazione del progetto e/o non corretta rendicontazione finale del progetto;
2. rideterminazione del contributo per irregolarità riscontrate a seguito di controlli a qualsiasi titolo effettuati, per le quali non si procede a revoca totale.

Nei casi di cui al comma precedente la Regione Toscana, previo contraddittorio con il Capofila, potrà procedere alla revoca parziale dell'agevolazione.
La difforme o parziale realizzazione del progetto costituisce ipotesi di adempimento difforme/parziale della Convenzione e, come tale sarà sottoposta all'approvazione del Dirigente responsabile del settore Consulenza giuridica e supporto alla ricerca in materia di salute.
Nel caso in cui vi sia stata erogazione da parte della Regione Toscana, con il provvedimento di revoca è disposta la restituzione delle somme erogate, maggiorate degli interessi maturati al Tasso Ufficiale di Riferimento (d'ora in avanti "TUR").
Nel caso in cui alla data della revoca parziale le erogazioni siano in corso, l'ammontare da recuperare sarà detratto a valere sull'erogazione ancora da effettuare. Nel caso in cui le erogazioni ancora da effettuare risultino di ammontare inferiore a quello da recuperare o nel caso in cui si sia già provveduto all'erogazione a saldo, sarà avviata una procedura di recupero (anche coattivo secondo quanto disposto dalla legge di contabilità della Regione e dal regolamento di attuazione) nei confronti dei componenti dell'ATS interessati.

Art. 14 - Trattamento dei dati personali

I dati dei quali la Regione Toscana entra in possesso a seguito della partecipazione al Bando Ricerca Salute 2018 e per la sottoscrizione della presente Convenzione, verranno trattati nel rispetto della vigente normativa di cui al D.Lgs. 196/2003 e successive modifiche ed integrazioni e al GDPR (Regolamento UE 2016/679).
A tal fine si fa presente che:

- La Regione Toscana- Giunta regionale è il titolare del trattamento (dati di contatto: P.zza Duomo 10 - 50122 Firenze; regionetoscana@postacert.toscana.it)

- Il conferimento dei dati, che saranno trattati dal personale autorizzato con modalità manuale e informatizzata, è obbligatorio ed il loro mancato conferimento preclude i benefici derivanti dal Bando. I dati raccolti non saranno oggetto di comunicazione a terzi, se non per obbligo di legge.
- I dati saranno conservati presso gli uffici del Responsabile del procedimento (Settore Consulenza giuridica e supporto alla ricerca in materia di salute) per il tempo necessario alla conclusione del procedimento stesso, saranno poi conservati in conformità alle norme sulla conservazione della documentazione amministrativa.
- L'interessato ha il diritto di accedere ai dati personali che lo riguardano, di chiederne la rettifica, la limitazione o la cancellazione se incompleti, erronei o raccolti in violazione della legge, nonché di opporsi al loro trattamento per motivi legittimi rivolgendo le richieste al Responsabile della protezione dei dati (*urp* dpo@regione.toscana.it*)*.
- L'interessato può inoltre proporre reclamo al Garante per la protezione dei dati personali, seguendo le indicazioni riportate sul sito dell'Autorità (http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/4535524)

Art. 15 - Registrazione e oneri fiscali

La presente Convenzione sarà registrata solo in caso d'uso ai sensi del D.P.R. n. 131/1986 a cura e spese della parte richiedente.
Ogni altra spesa relativa alla presente Convenzione, in qualunque tempo e a qualsiasi titolo accertate, è a carico del Capofila.

Art. 16 - Foro competente

Per qualsiasi controversia derivante o connessa alla presente Convenzione, ove la Regione Toscana sia attore o convenuto, è competente il Foro di Firenze, con espressa rinuncia a qualsiasi altro.

Art. 17 - Norme di rinvio

Per tutto quanto non espressamente previsto dalla presente Convenzione e dal Bando, si richiamano le norme comunitarie, nazionali e regionali vigenti in materia.

LETTO, APPROVATO E SOTTOSCRITTO

REGIONE TOSCANA
Il dirigente

NANNICINI ELISA
21.09.2022
09:25:02
GMT+00:00

IL Capofila
Il legale rappresentante

DAMONE ROCCO
DONATO
Regione Toscana
15.09.2022
14:39:46
GMT+01:00

ALLEGATI:

1) Scheda tecnica di Progetto;
2) Piano finanziario di Progetto;
3) Accordo di proprietà intellettuale definitivo;

ALLEGATO B

BANDO RICERCA SALUTE 2018

PROJECT DATA SHEET

SECTION 1 – GENERAL INFORMATION

Project title

Tuscany project to investigate on efficacy and safety of **C**annabis phytotherapic preparations for the treatment of **A**romatase i**N**hibitor-induced chronic resista**N**t p**A**in in **B**reast cancer pat**I**ents: a prospective multicenter randomized placebo-controlled phase III **S**tudy.

Project acronym

TosCANNABIS

Project coordinator (Principal investigator of the Lead Partner)

Dr Fabio Firenzuoli – AOU Careggi

Term (in months – max 36 months)

36

Indicate thematic line (indicate only one line)	☐ *1. Precision Medicine* ☐ *2. Organizational and management research* ☐ *3. Research in oncology:* ☐ *3.1 Biomedical research* ☐ *3.2 Translational and clinical research* ☐ *3.3 Epidemiologic research and prevention* *X 3.4 Complementary and integrated medicine* ☐ *3.5 Organizational and management research* ☐ *3.6 Rare tumors*

Project keywords

Cannabis, pain, breast cancer, aromatase inhibitors, randomized clinical trial

Abstract *EN* *(max 3000 characters, spaces included)*

Galenic preparations of “medical Cannabis” can be prescribed for the treatment of chronic cancer pain (or not) to patients resistant to conventional therapies. Pain associated to the aromatase inhibitor (AI) use is a common problem in breast cancer survivors determining patients’ noncompliance with AI therapy: an appropriate evidence-based strategy for management of AI-induced pain in breast cancer survivors is needed. Thus, the idea originating the Project is to evaluate the role of medical Cannabis in the treatment of AI-induced pain.

The primary objective of the project is to assess the efficacy and safety of Cannabis when added to the usual care of chronic pain induced by the aromatase inhibitors in breast cancer patients. To achieve this goal, a prospective multicenter placebo-controlled double-blind randomized phase III

study with a 1-year follow-up will be conducted in two clinical centers (AOUC and ISPRO) across Tuscany Region in the 36 months of the project. The University of Florence in collaboration with the Istituto Superiore di Sanità will accomplish safety assessment.

Women aged 18 years or older with a diagnosis of breast cancer, treated with AIs, presenting themselves at the hospital departments for chronic pain will be enrolled. The recruitment will be on a consecutive basis after obtaining written informed consent, given patient compliance with the in- and exclusion criteria, in a ratio of 1 (usual care plus placebo) to 1 (usual care plus Cannabis oil). Herbal Cannabis FM-2 (containing THC 5% - 8% and CBD 7.5% - 12%) will be provided by Istituto Farmaceutico Militare and a concentrated Cannabis extract (Cannabis oil) will be prepared and dispensed by the hospital pharmacy of Azienda USL Toscana Centro. Commercial Cannabis placebo will be used.

Secondary objectives are:
- to evaluate the impact of pain on the quality of life of patient;
- to examine the pharmacokinetics of Cannabis (i.e. THC, CBD and myrcene blood concentration);
- to explore Cannabis preparations in terms of active principles composition;
- to evaluate adherence to aromatase inhibitor therapy

Azienda USL Toscana Centro will conduct the chemical and biological analyses.

The synergy of researchers from different fields (clinical phytotherapy, pharmacology, toxicology, oncology, ginecology, chemistry, pharmacy and epidemiology) and the scientific collaboration with the MD Anderson Cancer Center has an excellent potential to develop an integrative pain treatment by the pharmacological exploitation of Cannabis galenic preparations with possible positive effects on the therapeutic path for women with breast cancer.

Abstract *IT* *(max 3000 characters, spaces included)*

I preparati galenici a base di "Cannabis medicinale" possono essere prescritti per il trattamento del dolore cronico oncologico (e non) a pazienti resistenti alle terapie convenzionali. Il dolore associato all'uso degli inibitori dell'aromatasi (IA) è un problema comune nei sopravvissuti al cancro al seno che spesso determina la non aderenza alla terapia con IA. Quindi, è necessaria un'appropriata strategia basata sull'evidenza per la gestione di questo tipo di dolore. L'idea che ha dato origine al progetto è di valutare il ruolo della Cannabis medicinale per il trattamento del dolore indotto da IA.

L'obiettivo principale del progetto è valutare efficacia e sicurezza della Cannabis in aggiunta al trattamento standard del dolore cronico indotta dagli inibitori dell'aromatasi nei pazienti con cancro mammario. Per raggiungere questo obiettivo, uno studio prospettico multicentrico randomizzato in doppio cieco controllato con placebo con un follow-up di 1 anno sarà condotto in due centri clinici (AOUC e ISPRO) della Regione Toscana nei 36 mesi del progetto. La valutazione della sicurezza verrà effettuata dall'Università di Firenze in collaborazione con l'Istituto Superiore di Sanità.
Le donne di età pari o superiore a 18 anni con una diagnosi di carcinoma mammario, trattate con inibitori dell'aromatasi, che si presentano presso i reparti ospedalieri per il dolore cronico, saranno reclutate su base consecutiva dopo aver ottenuto il consenso informato scritto, in conformità ai criteri di inclusione ed esclusione, in un rapporto di 1 (trattamento standard più placebo) a 1 (trattamento standard più olio di Cannabis). Le infiorescenze di Cannabis FM-2 (THC 5% - 8% e CBD 7.5% - 12%) saranno fornite dall'Istituto Farmaceutico Militare ed un estratto concentrato di Cannabis (olio di Cannabis) sarà preparato e distribuito dalla farmacia ospedaliera dell'Azienda USL Toscana Centro. Verrà utilizzato un placebo commerciale della Cannabis.

Gli obiettivi secondari sono:
- valutare l'impatto del dolore sulla qualità della vita del paziente;

- determinare la farmacocinetica della Cannabis (cioè concentrazione di THC, CBD e mircene nel sangue);
- analizzare i preparati di Cannabis in termini di composizione dei principi attivi;
- valutare l'aderenza alla terapia con IA.

Le analisi chimiche e biologiche saranno condotte dall'Azienda USL Toscana Centro.

La sinergia di ricercatori provenienti da diversi campi (fitoterapia clinica, farmacologia, tossicologia, oncologia, ginecologia, chimica, farmacia ed epidemiologia) e la collaborazione scientifica con il MD Anderson Cancer Center ha un eccellente potenziale per sviluppare un trattamento integrativo del dolore attraverso l'utilizzo farmacologico di preparati galenici di Cannabis, con possibili effetti positivi sul percorso terapeutico delle donne con carcinoma mammario.

Total project cost

Euro 350.000

SECTION 2 – MASTER DATA (this Section 2 must be filled in Italian)

LISTA DEI SOGGETTI COSTITUENTI IL PARTENARIATO
LIST OF PARTNERS

N°	Responsabile scientifico [1] Scientific Leader [2]	Aziende USL - AOU – enti del SSR – organismi di ricerca Regional Healthcare System organization (AUSL / AOU) – Research Organization	Ruolo (*) Role
1	Dr Fabio Firenzuoli	**AOUC**: Azienda Ospedaliero-Universitaria Careggi, Firenze	Principal Investigator Patient Recruitment and Management
2	Dr Sandra Catarzi	**ISPRO**: Istituto per lo studio, la prevenzione e la rete oncologica	Patient Recruitment
3	Dr Irene Ruffino	**AUTC**: Azienda USL Toscana Centro	Cannabis oil preparation Pharmacokinetic analyses / Chemical analyses
4	Prof Alfredo Vannacci	**UNIFI**: Department of Neurosciences, Psychology, Drug Research and Children's Health (NeuroFarBa), University of Florence	Pharmacovigilance Phytovigilance Data analysis

LISTA DI EVENTUALI SOGGETTI PARTECIPANTI AL PROGETTO – ORGANISMI DI RICERCA NAZIONALI ED INTERNAZIONALI (art. 4 del Bando)
LIST OF PARTICIPANTS

[1] il responsabile scientifico individuato dal capofila assume il ruolo di Coordinatore Scientifico del progetto

[2] The scientific leader identified by the lead partner assumes the role of Scientific Coordinator of the project

ALLEGATO B

BANDO RICERCA SALUTE 2018

EXTERNAL RESEARCH ORGANISATIONS (art. 4 of the Call)

N°	Denominazione organismo ricerca /Name of Research organization
1	Istituto Superiore di Sanità, ISS Dr Menniti, Da Cas, Massari
2	MD, ANDERSON Dr Lorenzo Cohen

(*) Nella ricerca possono essere coinvolti soggetti con i seguenti ruoli (art. 3 del Bando):

a) capofila:
b) partner

the research project may involve subjecs with the following roles (art. 3 of the Call): a) leader b)partner

FORMA ASSOCIATIVA DEI PARTNERS SCELTA:
ASSOCIATIVE FORM CHOSEN BY PARNERS:

- ☐ ATS costituita/constitued
- X ATS da costituire/to be consitued
- ☐ Altro (specificare)/Other

(specify)…….

SOGGETTO CAPOFILA/LEAD PARTNER

Ente/Organization	AOU Careggi Firenze
Rappresentante legale **Legal representative**	
Nome e cognome First name and surname	Rocco Donato Damone
Ruolo nell'ente Role in the organization	Direttore Generale
Responsabile scientifico/Coordinatore **Scientific Leader / Coordinator**	
Nome e cognome First name and surname	Fabio Firenzuoli
Ruolo nell'ente Role in the organization	Dirigente Medico Responsabile Centro di Ricerca e Innovazione in Fitoterapia e Medicina Integrata (CERFIT)
e-mail	fabio.firenzuoli@unifi.it
telefono/Phone number	3665645891
Curriculum Vitae del responsabile scientifico Curriculum Vitae of the Scientific Leader	allegare CV in inglese attach CV in English

PARTNER

Aggiungere una tabella per ogni partner indicato nella tabella "Lista dei soggetti costituenti il partenariato"

Add a table for each partner listed in the table "List of partners".

Ente/Organization	Università degli Studi di Firenze (Dip NeuroFarBa)
Rappresentante legale **Legal representative**	
Nome e cognome	Prof Patrizio Blandina

First name and surname	
Ruolo nell'ente Role in the organization	Direttore di Dipartimento NeuroFarBa
Responsabile scientifico **Scientific Leader**	
Nome e cognome First name and surname	Prof Alfredo Vannacci
Ruolo nell'ente Role in the organization	Professore Associato
e-mail	alfredo.vannacci@unifi.it
telefono/Phone number	3470465493
Curriculum Vitae del responsabile scientifico Curriculum Vitae of the Scientific Leader	allegare CV in inglese attach CV in English

Ente/Organization	**Istituto per lo studio, la prevenzione e la rete oncologica** (ISPRO)
Rappresentante legale **Legal representative**	
Nome e cognome First name and surname	Prof Gianni Amunni
Ruolo nell'ente Role in the organization	Direttore Generale
Responsabile scientifico **Scientific Leader**	
Nome e cognome First name and surname	Sandra Catarzi
Ruolo nell'ente Role in the organization	Dirigente Medico
e-mail	s.catarzi@ispro.toscana.it
telefono/Phone number	0557972594
Curriculum Vitae del responsabile scientifico Curriculum Vitae of the Scientific Leader	allegare CV in inglese attach CV in English

Ente/Organization	**Azienda USL Toscana Centro**
Rappresentante legale **Legal representative**	
Nome e cognome First name and surname	Dott Paolo Morello Marchese
Ruolo nell'ente Role in the organization	Direttore Generale
Responsabile scientifico **Scientific Leader**	
Nome e cognome First name and surname	Irene Ruffino
Ruolo nell'ente Role in the organization	Direttore Laboratorio Galenico di Santa Maria Nuova
e-mail	irene.ruffino@uslcentro.toscana.it
telefono/Phone number	055 6938971 - 055 6938346
Curriculum Vitae del responsabile	allegare CV in inglese

scientifico Curriculum Vitae of the Scientific Leader	attach CV in English

ORGANISMO DI RICERCA NAZIONALE/INTERNAZIONALE PARTECIPANTE
EXTERNAL RESEARCH ORGANIZATION

Aggiungere una tabella per ogni OR indicato nella tabella "Lista dei soggetti partecipanti al progetto"

Add a table for each External Research Organization listed in the table "List of participants"

Ragione sociale Name of organization	Istituto Superiore di Sanità (ISS)
Partita IVA /C.F (o analogo) VAT number / Fiscal Code (or the like)	03657731000 / 80211730587
Indirizzo/Address	Viale Regina Elena, 299 – 00161 Roma
e-mail	
Telefono/Phone number	06 4990
PEC	protocollo.centrale@pec.iss.it
Rappresentante legale **Legal representative**	
Nome e cognome First name and surname	
e-mail	
telefono/Phone number	
PEC	
Referente per il progetto se diverso dal rappresentante legale **Contact person for the project** **(if different from the legal representative)**	
Nome e cognome First name and surname	Dott Patrizia Popoli
Ruolo nell'organizzazione Role in the organization	Responsabile del Centro Nazionale per la Ricerca e la Valutazione preclinica e clinica dei Farmaci ISS, Roma
e-mail	patrizia.popoli@iss.it
telefono/Phone number	+39 06 4990 2482
PEC	

Ragione sociale Name of organization	The University of Texas - MD Anderson Cancer Center
Partita IVA /C.F (o analogo) VAT number / Fiscal Code (or the like)	EIN 74-6001118
Indirizzo/Address	1515 Holcombe Blvd, 77030 – Houston, Texas

e-mail	https://www.mdanderson.org/about-md-anderson/contact-us/askmdanderson/ask-a-question.html
Telefono/Phone number	1-877-632-6789
PEC	
Rappresentante legale **Legal representative**	
Nome e cognome First name and surname	
e-mail	
telefono/Phone number	
PEC	
Referente per il progetto se diverso dal rappresentante legale **Contact person for the project** **(if different from the legal representative)**	
Nome e cognome First name and surname	Lorenzo Cohen
Ruolo nell'organizzazione Role in the organization	Director of the Integrative Medicine Program
e-mail	lcohen@mdanderson.org
telefono/Phone number	1-877-632-6789
PEC	

ALLEGATO B

BANDO RICERCA SALUTE 2018

SECTION 3 – PROJECT DESCRIPTION

Idea originating the Project:
Galenic preparations of "medical Cannabis" can be prescribed for the treatment of chronic cancer pain to patients resistant to conventional therapies. Pain associated to the aromatase inhibitor (AI) use is a common problem in breast cancer survivors determining patients' noncompliance with AI therapy: an appropriate evidence-based strategy for management of AIA in breast cancer survivors is needed. Thus, the idea originating the Project is to evaluate the role of medical Cannabis in the management of AI-induced pain.

State of the art and preliminary data:
Aromatase inhibitors (AIs) are used in patients with breast cancer to decrease the risk of recurrence and to improve survival with less risk of the complications (such as vaginal bleeding and thrombosis) associated with endocrine treatment. Treatment with an AI usually continues for at least 5 years, so compliance cannot be ignored in this patient population (Kim *et al.*, 2018).

AI-associated arthralgia (AIA) is a common problem in breast cancer survivors, it is associated with noncompliance with aromatase inhibitor therapy, and may deter physicians from prescribing an AI fearing the risk of permanent joint damage (Coleman *et al.*, 2008). AIA is a joint pain disorder able to inhibit breast cancer clinical diagnosis and treatment. In fact, symptom relief or deterioration is closely associated with AIs use or discontinuation. The prevalence of AIA in postmenopausal women with breast cancer is reported to be in the order of 20–70%. Several mechanisms have been reported for the onset of AIA: estrogen depletion (Islander *et al.*, 2011), reduced IL-6 expression (Le Bail *et al.*, 2001), bone alterations, activation of pain transmission pathways and neurogenic inflammation (Fusi *et al.*, 2014). However, AIA aetiology and pathological mechanism have not been definitely clarified, so its management remains unclear (Kim *et al.*, 2018).

A specific management algorithm for AIA based on clinical experience has been proposed (Coleman *et al.*, 2008). It recommends a sequential approach to disease management, involving patient lifestyle modification in addition to taking a stratified approach to pharmacological intervention starting with NSAIDs and changing to alternative breast cancer treatment if necessary. Given that AIA is common in breast cancer survivors and affects their quality of life, evidence on the therapeutic options available is urgently needed to be able to formulate a long-term management plan for this patient population (Kim *et al.*, 2018).

Actually, the treatment of chronic cancer pain is based on a combination of pharmacotherapy and complementary non-medicated approaches such as acupuncture, physical therapy, in addition to psychological or behavioural approaches (Blake *et al.*, 2017). The pharmacological approach for the relief of chronic pain is based primarily on pain intensity. This approach determines that mild pain should be treated with "simple" analgesics (*e.g.,* acetaminophen, or non-steroidal anti-inflammatory drugs, NSAIDs), whereas moderate to severe pain should be treated with opioids (Aviram *et al.*, 2017). Opioid use has become a highly controversial topic due to the wide range of problems it presents. This can be due to a combination of factors, including differences in individual responses to these drugs, and the presence of serious side effects such as severe constipation. Patients who do not respond well to opioid analgesics, or have severe side effects from the use of traditional analgesics are in need of alternative therapeutic options (Blake *et al.*, 2017).

Recently, compounds derived from the plant species *Cannabis Sativa* L. have demonstrated the potential to alleviate pain. The most commonly studied examples include tetrahydrocannabinol (THC), and cannabidiol (CBD) from the family of compounds known as cannabinoids. Several pre-

clinical studies have been conducted in animal models, investigating the mechanism of cannabinoid modulation of pain pathways One of the identified mechanisms is the interaction of these compounds with one of the body's endogenous signalling systems, known as the "endocannabinoid" system. This system acts independently of the opioid pathway to control pain signalling, immune activation, and inflammation (Blake *et al.*, 2017). A conclusive review and meta-analysis, which incorporates 43 (2.437 patients) randomized placebo-controlled trials (RCTs) regarding the efficacy of cannabis-based medicines (CBMs) for chronic pain treatment has been conducted (Aviram *et al.*, 2017). There is evidence suggesting that medical cannabis reduces chronic or neuropathic pain in advanced cancer patients. However, the results of many studies lacked statistical power, in some cases due to limited number of study subjects. Therefore, there is a need for the conduct of further double-blind, placebo-controlled clinical trials with large sample sizes in order to establish the optimal dosage and efficacy of cannabis-based therapies. As pain negatively influences the physical, functional, and emotional domains of life, effective pain management strategies are essential for restoring and maintaining quality of life of cancer patients.

The safety of cannabis use for medical purposes has not been systematically evaluated. Ware *et al.* (2015) have conducted a prospective cohort study to describe safety issues among individuals with chronic non-cancer pain. The primary outcome consisted of serious and not-serious adverse events (AEs). One hundred and fourty-one current users and 58 ex-users with chronic pain were recruited to the cannabis group and 216 individuals with chronic pain but no current cannabis users were included as controls. There has been no difference in risk of serious adverse events between groups but medical cannabis users have been at increased risk of non-serious adverse events from mild to moderate ones. Thus, herbal cannabis has appeared to have a reasonable safety profile.

In palliative care, cannabis and cannabinoids are considered as add on therapy for cancer pain in persons without sufficient relief from opioids or other established analgesics. Cannabis-based medicines can be considered as third line therapy for chronic neuropathic pain since some studies demonstrate weak evidence of their efficacy in neuropathic pain. On the other hand, cannabis role and appropriate use for the management of chronic pain in musculoskeletal conditions has not been investigated (Perrot *et al.,* 2017). Natural phytocannabinoids and synthetic derivatives have produced clear activity in a variety of models of joint pain in animals. These effects are the result of both inhibition of pain pathway signalling (mostly CB1) and anti-inflammatory effects (mostly CB2). Preclinical data has clearly demonstrated that the different elements of the endocannabinoid signaling system are expressed in the appropriate tissues in humans and animals and that cannabinoids do produce beneficial effects in animal models of joint pain. Therefore, the situation should certainly be viewed as promising. Another thing that is not clear is whether CB1 active cannabinoids such as THC are essential for producing analgesic effects or whether non-psychotropic substances such as CBD are also helpful. Clearly, it would be advantageous to have peripherally active cannabinoids, or non-psychotropic molecules that really benefited patients (Miller & Miller, 2017). In view of the considerable limitations of the available studies and according to the conclusions of several meta-analyses (Häuser *et al.*, 2018; Whiting *et al.,* 2015), it is not currently possible to assess the efficacy of cannabis for musculoskeletal pain. There is a need for well-controlled clinical trials since there are very few effective analgesics in musculoskeletal conditions and new pharmacological analgesic approaches, including cannabis and cannabis-based drugs, can be very important (Perrot *et al.,* 2017).

Cannabis-based medicines have been approved for pain management in a number of countries.
The cannabis extract nabiximol is the most prevalent cannabis-based medicinal product marketed in Europe. Synthetic cannabinoids and standardized cannabis are less prevalent, and no country allows the growing of cannabis for personal medical use. The bringing of medical cannabis products from across borders to countries where the drug is not marketed is quite limited. There is only limited use of the cannabis plant as such for medical purposes, possibly indicating a different scenario in Europe

as compared to the USA (Bramness JG et al., 2018). EUFAS (European Federation for Addiction Societies, Barcelona, Spain) as an umbrella association of addiction societies stresses the need for further studies on the efficacy of medical cannabis and warrants for possible dangers associated with the increasing popularity of medical cannabis. For example, it is recommendable a regulation at European level concerning registration and medical indications, development of uniform compounds and strength of products, and rules concerning sales and marketing.

Cannabis in Italy

Since 2006 in Italy doctors can prescribe galenical preparations, to be set up by the pharmacist in pharmacies, using the active substance obtained from the inflorescences of cannabis cultivated with the authorization of a National Cannabis Organism, dried and ground, to be taken in the form of decoction or inhalation with a special vaporizer or other approved preparation. From 2013 in Italy, neurologists also prescribe a product registered as a medicine based on cannabis extracts to reduce painful spasms in multiple sclerosis.

Until now, only products sold by the Office of Medicinal cannabis (Dutch organization for cannabis) of the Dutch Ministry of Health were imported into Italy for the preparation of masterly preparations with cannabis-based plant products, according to the procedure for import provided by the Ministerial Decree 11/2/97. In 2016, our country started a national production of cannabis for medical use at the "Istituto Farmaceutico Militare" of Florence (SCFM), thanks to the collaboration between the Ministry of Health and the Ministry of Defense, in order to guarantee access to such therapies at adequate and safe costs. This is the product Cannabis FM-2 (containing THC 5% - 8% and CBD 7.5% - 12%), the first active substance based on cannabis produced in accordance with European directives on medicines (EU-GMP) on a deposited and controlled production process, in a pharmaceutical workshop authorized by AIFA and whose distribution is authorized by the State Organization for Cannabis at the Ministry of Health. The prescription of cannabis for medical use in Italy concerns the use in chronic pain, in pain associated with multiple sclerosis and spinal cord injury; in nausea and vomiting caused by chemotherapy, radiotherapy, HIV therapy; as a stimulant of appetite in cachexia, anorexia, loss of appetite in cancer patients or patients with AIDS and in anorexia nervosa; the hypotensive effect in glaucoma; the reduction of involuntary body and facial movements in the Gilles de la Tourette syndrome (DM 9/11/2015).

The more recent Document "Raccomandazioni per il medico prescrittore di sostanza vegetale cannabis FM2 infiorescenze" (approved in February 2017 by a specific working group nominated in 2014 according to Ministery of Health and Ministery of Defence, the same who worked on the Decree), is addressed to physician and is more detailed and updated in medical issues, regarding in particular Cannabis FM2 produced by "Istituto Farmaceutico Militare" in Florence (the only authorized for farming in Italy).

Tuscan county

The Tuscany Region has established the rules for the administration of therapeutic cannabis with a specific resolution, which dictates the procedural and organizational guidelines for the implementation of regional law n. 18, of May 2012. The law provides that the Region protects the principles of autonomy and responsibility of the medical doctor in the therapeutic choice, and scientific evidence, and consequently dictated the organizational provisions related to the use of cannabinoid drugs for medicinal purposes by the operators and structures of the regional health service.

The resolution establishes that all physicians are able to prescribe cannabis preparations, within the limits established by the national legislation in force. The prescription and initiation of treatment with these medicines must be performed in hospitals (or similar) of the regional health service, including inpatient wards, day-hospital or outpatient facilities. In case there is a need to continue the treatment even after hospitalization, the doctor or the structure can carry out an assisted discharge of the patient and provide directly to the delivery of drugs considered necessary for the continuation of drug therapy. Hospital pharmacies must activate all the procedures related to the purchase (and import

whether necessary) of medicinal substances and the setup of galenic preparations.
For some categories of patients, Cannabis is administered free of charge to the Regional Health Service (when a treatment with non-steroidal anti-inflammatory drugs or with cortisone or opioid drugs was ineffective).

General goal of the Project and related strategy / experimental design:
The primary objective is to assess the effectiveness of cannabis and the risk of adverse events associated with cannabis when added to the standard treatment of chronic pain induced by the aromatase inhibitors in breast cancer patients.

To achieve this goal, a prospective multicenter placebo-controlled double-blind randomized phase III study with a 1-year follow-up will be conducted in two clinical centers (AOUC and ISPRO) across Tuscany Region in the 36 months of the project.

Patient recruitment will be carried out by
AOUC

1. Center of Research and Innovation in Phytotherapy and Integrative Medicine (CERFIT, AOUC), Responsible Dott. Fabio Firenzuoli, Physician Dr Francesco Sivelli;
2. SOD Palliative care and clinic of Pain (AOUC) Resp. Dr. Rocco Domenico Mediati;
3. Section of Gynecology and Obstetrics, Department of Woman and Child Health (AOUC), Dr Angela Maria Becorpi;
4. Department of Radiation Oncology (AOUC), Director Prof. Lorenzo Livi, Clinician Dr Icro Meattini;
5. Breast Unit (AOUC), Responsible Dr Catia Angiolini;

ISPRO

6. Senology Unit (ISPRO), Director Dr Beniamino Brancato, Scientific Leader Dr Sandra Catarzi, Physician Dr Giulia Picozzi.

Women aged 18 years or older with a diagnosis of breast cancer, treated with aromatase inhibitors presenting themselves at the hospital departments for chronic pain will be enrolled. The recruitment will be on a consecutive basis after obtaining written informed consent, given their compliance with the in- and exclusion criteria, in a ratio of 1 (usual care) to 1 (usual care plus Cannabis oil).

Herbal Cannabis FM-2 (containing THC 5% - 8% e CBD 7.5% - 12%) will be provided by Istituto Farmaceutico Militare and a concentrated cannabis extract (cannabis oil) will be prepared and dispensed by the hospital pharmacy of Azienda USL Toscana Centro. Commercial placebo versions of many Cannabis strains are available for use in clinical studies. Placebo cannabis is produced by selectively removing the biologically active cannabinoids (like THC and CBD) while maintaining the original terpene content. Consequently, placebo cannabis will look like cannabis, but also carry its taste and smell which is derived from the cannabis terpene content.

Secondary objectives are:
- to evaluate the impact of pain on the quality of life of patient
- to examine the pharmacokinetics of cannabis (i.e. THC, CBD and myrcene blood concentration);
- to explore cannabis preparations in terms of active principles composition;
- to evaluate adherence to aromatase inhibitor therapy.

The chemical and biological analyses to accomplish these goals will be conducted by Azienda USL Toscana Centro.

Operational Objectives:
(up to 12 operational objectives)

Operational Objective 1 (OO1): Study Population

- Activity 1.1

Recruitment of the patients.

Women will be enrolled for the entire duration of the study according to the hospital clinical activities. Before the participation, the aims of the study will be explained and written informed consent will be requested. In the first 18 months of the study at least 170 patients will be recruited (see *Power of the study and sample size calculation* above).

Inclusion criteria:

- Women
- 18 years of age
- Breast cancer patients
- In therapy with aromatase inhibitors
- Patients with chronic pain
- Resistant pain to conventional therapies
- Signed informed consent and privacy protection

Exclusion criteria:

- Male
- Women < 18 years of age
- Mental alterations during brain development;
- Severe cardio-pulmonary disorders
- Severe liver failure, renal
- Chronic hepatitis C
- Personal history of psychiatric disorders or a family history of schizophrenia
- Previous history of drug addiction or abuse of psychotropic substances or alcohol;
- Maniac depressive disorders;
- Patients treated with sedative, antidepressant or psychoactive hypnotic drugs
- Pregnant or nursing women;
- No compliance to study procedure for medical judgement
- No use of Cannabis for other diseases the last 3 months

Patient recruitment will be carried out by

AOUC

1. Center of Research and Innovation in Phytotherapy and Integrative Medicine (CERFIT, AOUC), Responsible Dott. Fabio Firenzuoli, Physician Dr Francesco Sivelli;
2. SOD Palliative care and clinic of Pain (AOUC) Resp. Dr. Rocco Domenico Mediati;
3. Section of Gynecology and Obstetrics, Department of Woman and Child Health (AOUC), Dr Angela Maria Becorpi;
4. Department of Radiation Oncology (AOUC), Director Prof. Lorenzo Livi, Clinician Dr Icro Meattini;
5. Breast Unit (AOUC), Responsible Dr Catia Angiolini;

ISPRO

Senology Unit (ISPRO), Director Dr Beniamino Brancato, Scientific Leader Dr Sandra Catarzi, Physician Dr Giulia Picozzi.

Power of the study and sample size calculation

The power of the study is calculated for pain relief analysis considered as a continuous variable

(variation of the VAS score) outcome, assuming that the 60% of patients treated with cannabis decreases from mean VAS=6.5 to mean VAS=3.5 and the remaining 40% has no pain relief as well as the not-treated group (data not published; Mediati RD, 2018).

Present study has 90% power to detect a minimum difference in pain relief between study arm 1 and arm 2 (as reported in the following table), assuming α= 0.05 and a 20% correlation between group pre-intervention and post-intervention, with co-variance analysis comparing final mean values of the two studied groups adjusted for the baseline values.

Expected minimum variation between two study arms (VAS score)	Expected standard deviation	Sample size (N/arm)	Total sample size (N)
2 points	2.0	23	46
2 points	1.5	13	26
1 point	**2.0**	**83**	**166**
1 point	1.5	48	96

Thus, we will recruit at least 85 patients for study arm to be able to point out up to the minimum variation in VAS score.

Randomization of the patients
Our trial is with parallel design: each group of participants receives a different intervention. Two-arm study design: the treaty group receives the experimental intervention and the controls group the placebo treatment. Patients will be assigned to one of the two groups by simple randomization. This clinical trial is prospective, placebo-controlled, randomized, double-blind.
The trial will be conducted according to globally accepted standards of good clinical practice and in keeping with local regulations, and approved of the designated ethics committees of all centers.
Informed consent in written form has to be given before the first study-specific action either by patient's themselves or patient's legal representatives.
A central managing pharmacy acting independently from the principle investigator and the study centers will be responsible for study drug blinding and study drug logistics. Institutional, logistical and geographical division of study pharmacy ensures blinding of the study personnel and the patients. Allocation to treatment group is done chronologically using a pre-defined randomization list, which was delivered to the pharmacy for blinding the study medication.

Arm 1 patients:
usual care
+ Placebo treatment: Average dosage: placebo oil 15 drops morning and evening
This dosage will be reached gradually during the first month of therapy.

Arm 2 patients:
usual care
+ Cannabis treatment: Average dosage: Cannabis oil 15 drops morning and evening
This dosage will be reached gradually during the first month of therapy.

- Activity 1.2
Information retrieval.
A structured questionnaire will be administered, by a specifically trained monitor, to patients. The questionnaire will include data on socio-demographic information (age, gender, body mass index), medical history, coexisting illnesses, lifestyles and dietary habits, and use of non-conventional and conventional drugs. Data concerning the diagnosis of cancer and the evolution of the disease will be collected from medical records. Clinical information will be also used. Data on health conditions as

well as other parameters that are potentially predictive of higher or lower treatment responsiveness will be carefully collected with the aim of adjusting for any confounding variables and/or effect modifier. All information will be recorded in an individual Case Report Form (CRF) for each patient.

OO1 will be performed by
AOUC
1. Center of Research and Innovation in Phytotherapy and Integrative Medicine (CERFIT, AOUC), Responsible Dott. Fabio Firenzuoli, Physician Dott. Francesco Sivelli;
2. SOD Palliative care and clinic of Pain (AOUC) Resp. Dr. Rocco Domenico Mediati;
3. Section of Gynecology and Obstetrics, Department of Woman and Child Health (AOUC), Dr Angela Maria Becorpi;
4. Department of Radiation Oncology (AOUC), Director Prof. Lorenzo Livi, Clinician Dr Icro Meattini;
5. Breast Unit (AOUC), Responsible Dr Catia Angiolini;

ISPRO
Senology Unit (ISPRO), Director Dr Beniamino Brancato, Scientific Leader Dr Sandra Catarzi.

The monitor will be trained by **AOUC.**

Operational Objective 2 (OO2): Pain management

- Activity 2.1
Pain intensity assessment
A Visual Analogue Scale (VAS) will be used and completed by each patient. VAS requires to rate the pain from 0 to 10 (11-point visual scale), with the understanding that 0 represents the absence of pain and 10 represents the opposite extreme of pain intensity (*i.e*., pain as bad as it could be). The selected number represents their pain numerical rate.

- Activity 2.2
Pain treatment
Usual care
Analgesics may include paracetamol, the non-steroidal anti-inflammatory drugs, and opioid drugs. Integrative approaches include multivitamin supplements, acupuncture analgesia and physical activity

Arm 1 patients:
usual care
+ Placebo treatment: Average dosage: placebo oil 15 drops morning and evening
This dosage will be reached gradually during the first month of therapy.

Arm 2 patients:
usual care
+ Cannabis treatment: Average dosage: Cannabis oil 15 drops morning and evening
This dosage will be reached gradually during the first month of therapy.

OO2 will be performed by **AOUC**:
1. Center of Research and Innovation in Phytotherapy and Integrative Medicine (CERFIT, AOUC), Responsible Dott. Fabio Firenzuoli, Physician Dott. Francesco Sivelli;
2. SOD Palliative care and clinic of Pain (AOUC) Resp. Dr. Rocco Domenico Mediati;

Operational Objective 3 (OO3): Galenic formulations of Cannabis

- Activity 3.1

Olive oil (Ph.Eur.) extraction of female Cannabis inflorescence and placebo provided.

Herbal Cannabis FM-2 (contenente THC 5% - 8% e CBD 7,5% - 12%) will be provided by Istituto Farmaceutico Militare and a concentrated cannabis extract (cannabis oil) will be prepared:

1. Weigh Cannabis inflorescences to obtain a ratio of 1 g: 10 mL
2. Measure olive oil (Ph.Eur.) to obtain the ratio 1 g: 10 mL.
3. Finely chop the inflorescences.
4. Evenly distribute the inflorescences in a single layer (max height 1 cm) inside a reservoir.
5. Insert in a dry stove, not ventilated, with sensitivity +/- 1°C and with the possibility of reading from the outside, to the temperature of 115°C for 40 minutes.
6. Take away the reservoir and allow cooling for at least 10 minutes, keeping the container closed.
7. Transfer the Cannabis inflorescences into the olive oil (Ph.Eur.) at room temperature and finely chop by a turbo-emulsifier.
8. EXTRACTION: place the beaker, under continuous stirring, in a preheated water bath at a temperature of 100°C, maintaining constant the level and temperature of the heating liquid (100°C) throughout the extraction period (40 minutes).
9. FILTRATION: immediately collect the oil by filtration with a vacuum pump.
10. Take a 0.5 mL sample and send to the analysis laboratory.

Commercial placebo versions of many Cannabis strains are available for use in clinical studies. Placebo cannabis is produced by selectively removing the biologically active cannabinoids (like THC and CBD) while maintaining the original terpene content. Consequently, placebo cannabis will look like cannabis, but also carry its taste and smell which is derived from the cannabis terpene content.

- Activity 3.2

Cannabinoid determination in oil extract by HPLC/DAD
MP D031 Rev. 4 06/06/2017.

Cannabidiol (CBD), Cannabinol (CBN), Δ-9-tetrahydrocannabinol (THC), Δ-9-tetrahydrocannabinoic acid (THCA) and myrcene concentration in galenic oil preparations of cannabis will be determined using high-pressure liquid chromatography (HPLC) with a diode array detector (DAD). Briefly, the sample to test (0.04 ml) is placed in glass vials with 0.96 ml of tetrahydrofuran mixing with vortex. Then, 0.05 ml of this sample is added to 0.95 ml of Acetonitrile (ACN) and 0.01 ml are injected and analysed with:

- HPLC-DAD (Thermo-Fisher Surveyor Plus) equipped with quaternary pump, autosampler and UV DAD;
- Poroshell® 120 SB-C18 column (2.1 x 150 mm 2.7 micron) with pre-column, temperature 53.0°C.

Cannabinoid are identified by their retention time in comparison with the relative standard retention time. For quantitative determination, referral standard stock solutions of the test analytes are used to obtain the calibration curve. Calibration curve standards are prepared by adding increasing dose of standard to blank oil. Levels of calibration standards are in a range from 1 to 20 mg/ml for each analytes. In the analytical series are consecutively added the calibration points, a negative control and the test samples. The metrological error is about the 25% for each analyte. Excel Result calculation are computed by Excel (MPD031.xls).

OO3 will be carried out by **Azienda USL Toscana Centro**:

1. Laboratorio Galenico di Santa Maria Nuova, Director: Dr Irene Ruffino
2. SOS Tossicologia Clinica e Antidoping, Director: Dr Roberto Baronti

Operational Objective 4 (OO4): Pharmacokinetic evaluations

- Activity 4.1

Blood sample collection.

Patients will give their informed written consent to the project and agree to undergo blood sampling and pharmacokinetic analyses. Blood sample will be collected during the follow up visit T3 (see OO5) for the first 20 patients in each study arm.

- Activity 4.2

Cannabinoid determination in blood samples by LC-MS/MS.
MP D020 Rev. 13 24/09/2018

Cannabidiol (CBD), Cannabinol (CBN), Δ-9-tetrahydrocannabinol (THC), Δ-9-tetrahydrocannabinoic acid (THCA) and 11-hydroTHC concentration in blood samples will be determined by liquid chromatography tandem mass spectrometry (LC-MS/MS). Briefly, the whole-blood samples (0.2 mL) is placed in plastic 2.0-mL vials. The samples are precipitated with acetonitrile and the internal deuterated standard (e.g. THC-D3) mixing on a vortex mixer. After centrifugation, the organic solvent is transferred to a 2-mL GC glass vial and analysed in the LC-MS/MS system:

- 4000 Q trap system (ABsciex) constituted by HUPLC Ultimate3000 (Thermofisher), and a hybrid triple quadrupole linear ion trap MS;
- Poroshell® 120 SB-C18 column (2.1 x 150 mm 2.7 micron) with pre-column, temperature 40.0°C.

For quantitative determination, referral standard stock solutions of the test analytes are used to obtain the calibration curve. Calibration curve standards are prepared by adding increasing dose of standard to blank plasma. In the analytical series are consecutively added the calibration points, a negative control and the test samples. Furthermore, two positive controls at known analyte concentration are analysed. The metrological error is about the 25% for each analyte.

OO4 will be carried out by **AOUC** and **Azienda USL Toscana Centro**:

1. SOS Tossicologia Clinica e Antidoping, Director: Dr Roberto Baronti

Operational Objective 5 (OO5): Follow up

- Activity 5.1

Clinical visit at T0.

Each patient will be subjected to a baseline visit (T0), which will correspond to the selection visit to verify the inclusion and exclusion criteria of the protocol.
At the baseline visit, we will proceed to identify the inclusion criteria, usual care, obtain the informed written consent of the patient, fill in the medical record.
Administer Pain VAS Scale and Short Form - Brief Pain Inventory (SF-BPI)
Send for randomization

- Activity 5.2

Clinical visits from T1 to T6

Each patient will be subjected to the subsequent follow up visits:
T1: 7 days
T2: 14 days
T3: 30 days
T4: 3 months
T5: 6 months
T6: 12 months

At each follow-up visit, the following will be carried out:

registration of FOLLOW-UP visit
medical check-up:
VAS scale
Short Form - Brief Pain Inventory (SF-BPI)
Recordings of suspected adverse reactions
Record any changes to therapies in progress
Gradual adjustment of treatment dosage based on clinical conditions

OO5 will be performed by **AOUC**:

1. Center of Research and Innovation in Phytotherapy and Integrative Medicine (CERFIT, AOUC), Responsible Dott. Fabio Firenzuoli, Physician Dott. Francesco Sivelli;
2. SOD Palliative care and clinic of Pain (AOUC) Resp. Dr. Rocco Domenico Mediati;

Operational Objective 6 (OO6): Pharmacovigilance

- Activity 6.1

Safety assessment.

Investigators will be responsible for monitoring the safety of patients who enter this study. The investigator remains responsible for following Adverse events (AEs) and events that caused the patient to discontinue before completing the study. The patient should be followed until an AE is resolved.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures. All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 30 days after the last dose of therapy or until the last study visit, whichever period is longer. Adverse Events and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious. All SAEs must be reported to the Pharmacovigilance responsible person within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to therapy, action taken regarding with treatment, and outcome.

- Activity 6.2

AEs evaluation.

A qualified Investigator will evaluate all adverse events as to: intensity, causality, duration, action taken, outcome.

Intensity

The intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of CTCAE, Version 4.03

Causality

The Investigator must determine the relationship between the administration of protocol therapy and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: the temporal relationship of the adverse event to experimental therapy administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the adverse event to experimental therapy administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Action Taken
The Investigator will report the action taken with treatment because of an AE or SAE, as applicable (e.g., discontinuation or reduction of drugs, as appropriate) and report if concomitant and/or additional treatments were given for the event.

- Activity 6.3
AEs Reporting.
Pharmacovigilance responsible person will inform relevant Regulatory Authorities and Ethics Committees:
- Of all relevant information about serious unexpected adverse events suspected to be related to the treatment that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently be submitted within an additional eight days
- Of all other serious unexpected events suspected to be related to the treatment as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

OO6 will be performed by **UNIFI**:
1. Department NeuroFarBa, University of Florence, Scientific Leader: Prof Alfredo Vannacci, Participants: Dr Roberto Bonaiuti (Research Fellow, SCARAB LAB), Dr Niccolò Lombardi (Research Fellow)

Operational Objective 7 (OO7): Phytovigilance

- Activity 7.1
Cannabis Adverse Reactions (ARs) collection.
Within the Phytovigilance system, coordinated by the Italian National Institute of Health, will be collect the spontaneous reports of ARs occurred after the assumption/administration of cannabis preparations. Reports can be sent from anyone observing a suspected adverse reaction associated with these products by an ad hoc form, available on the websites of the involved institutions (National Institute of Health, Ministry of Health, Italian Medicines Agency) and online through VigiErbe website (www.vigierbe.it). All reports will be registered in a database at the National Institute of Health. Labels of the products will be provided by the Ministry of Health. Diagnosis will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 4).

- Activity 7.2
Cannabis ARs evaluation.
The spontaneous reports of ARs, occurred after the assumption/administration of cannabis preparations, will be evaluated once inserted in the Phytovigilance system, specific for Cannabis ARs, coordinated by the Italian National Institute of Health. A Scientific Committee, including experts in toxicology, pharmacology, pharmacognosy, phytotherapy, botany, pediatrics, homeopathy, has been appointed for the evaluation of the reports and the detection of risk signals. A Steering Committee with experts in pharmacovigilance, pharmacoepidemiology and regulatory aspects supports the activities of the Scientific Committee. For serious cases, follow-up of patients is obtained from the hospital physician.

OO7 will be performed by **UNIFI** in collaboration with the external research organization **ISS** Participants Dr Francesca Menniti Ippolito, Dr Roberto Da Cas, and Dr Marco Massari and with Dr Eugenia Gallo (University of Florence).

Operational Objective 8 (OO8): Data analysis

- Activity 8.1

Data entry.
During the period of recruitment, patients' data will be collected by a monitor and will be input into a dedicated database.

- Activity 8.2
Statistical data analysis.
Data analysis will be conducted starting from the end of the last patient follow up (from month 30 of the project).
Continuous variables will be reported as mean value and related standard deviation, or as median value and interquartile range, according to data distribution, and will be compared between the two intervention groups using the t-Student or the Mann-Whitney test, respectively.
Categorical variables will be reported as absolute numbers and percentages, and will be compared between the two intervention groups using the Chi-square test.
For the efficacy outcome, within each group of intervention, the mean (or median) variation of the VAS score at each time-point of follow-up as compared to the baseline score will be compared between the two interventions, using the t-Student or the Mann-Whitney test for unpaired data, respectively, and adjusting the analysis for the baseline values. The mean (or median) variation of the VAS score at each time-point of follow-up as compared to the baseline score will be compared between the two interventions, using the t-Student or the Mann-Whitney test for unpaired data, respectively.
As for the safety outcome, the occurrence of adverse events will be considered as a dichotomous variable (occurrence vs non-occurrence).
Proportions of patients experiencing at least one adverse events will be compared between the two intervention groups, using the Chi-square test.
Furthermore, conditioned logistic regression models will be fitted to estimate the risk (Odds Ratio and related 95% Confidence Interval (CI)), of adverse events among patients treated with cannabis as compared to usual care; models will be conditioned for the matching variables and adjusted for the demographic and clinical covariates recorded in Activity 1.2.
Statistical significance will be considered for p-value <0.05. Statistical analysis will be performed using the software STATA version 14.

OO8 will be performed by **UNIFI** in collaboration with the external research organization **ISS** Participants Dr Francesca Menniti Ippolito, Dr Roberto Da Cas, Dr Marco Massari.

Operational Objective 9 (OO9): Study results

- Activity 9.1
Discussion of the results.
Principal Investigator will take care to organize one meeting with all the participants working on the research every six months of the projects. During the first five meetings, all the scientific and practical aspects of the clinical study will be taken into account. During the last meeting, all the participants will discuss the results of the study.

- Activity 9.2
Final study report and dissemination of the results.
According to the ICH-GCP, the Principal Investigator will undertake to produce a report on the study, publish all the data collected as described in the Protocol and to ensure that the data are reported responsibly and consistently. In particular, the publication of data deriving from the present study and their dissemination to scientific congresses will take place independently of the results obtained. The transmission or dissemination of data, through scientific publications and / or presentation in congresses, conferences and seminars, participation in multicenter studies, will take place

exclusively following a purely statistical processing of the same, or in an anonymous form. Responsible for the entire research and therefore for the data processing is Dr. Fabio Firenzuoli, principal investigator of the study.

OO9 will be performed by **AOUC** (Dr Firenzuoli) that for the Activity 9.1 will collaborate with the external research organization **The University of texas, MD Anderson,** Prof Lorenzo Cohen.

For each Operational Objective, provide the required information:

Operational Objective no. (1)
Name: Study Population
Description of the operational objective:
Patient recruitment, Training of the monitor who will perform data collection, Information retrieval

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)

If yes, please indicate in which activity(ies):

At least 170 patients should be recruited and the relative questionnaire administered to reach the power of the study (see above).

X the objective includes check points (*milestones*)

If yes, please indicate in which activity(ies):

Each six months the number of recruited patients will be checked (at least 28 in arm 1 and 28 in arm 2).

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on during the first 30 months of the project.
Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 107.000

List of activities envisaged under the Operational Objective:
Activity no. 1.1 - Name: **Recruitment of the patients** *- Cost: euro* ***47.000***
Activity no. 1.2 - Name: **Information Retrieval** *- Cost: euro* ***60.000***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 1.1 - Name: Recruitment of the patients
Explain the individual activity
Physicians (AOUC, ISPRO) will recruit at least 170 patients and perform the relative basal clinical visit.
Activity no. 1.2 - Name: Information Retrieval
Explain the individual activity
A structured questionnaire will be administered, by a specifically trained monitor, to patients.

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities
Written informed consent will be requested to each patient.
The questionnaire will include data on socio-demographic information (age, gender, body mass index), medical history, coexisting illnesses, lifestyles and dietary habits, and use of non-conventional and conventional drugs.
All information will be recorded in an individual Case Report Form (CRF) for each patient.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*

Dr Firenzuoli 1
Dr Mediati 1
Dr Becorpi 2
Dr Angiolini 2
Dr Sivelli 1
Dr Meattini 2
Dr Picozzi 1

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*

Trained Monitor 31 ftpm

- *Total Personnel (full time person month)* 41 ftpm

Subcontracts:[3]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.

Principal Investigator will contact a notary for the ATS legal constitution.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

Present study has 90% power to detect a minimum difference of VAS=1 in pain relief between study arm 1 and arm 2 (with at least 85 recruited patients/each arm), assuming α= 0.05 and a 20% correlation between group pre-intervention and post-intervention, with co-variance analysis

[3] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

comparing final mean values of the two studied groups adjusted for the baseline values. Each six months the number of recruited patients will be checked (at least 28 in arm 1 and 28 in arm 2).

Timing:
Indicate the months during which the Activity will be carried out.

Months 1 – 30: activity 1.1 up to first 18 months and activity 1.2 up to the 30th month (see Gantt flowchart).

Operational Objective no. (2)
Name: Pain management
Description of the operational objective:
To assess pain intensity at basal level and follow up step (T1-3-6-12) for each patient.
To treat pain at basal level and follow up step, eventually adjusting the analgesic dose, in line with the treatment established for each arm of the study (usual care plus placebo vs usual care plus Cannabis)

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)
If yes, please indicate in which activity(ies):

At least 170 patients should be visited and treated and pain should be measured and the relative questionnaire administered

X the objective includes check points (*milestones*)
If yes, please indicate in which activity(ies):

Each six months the number of recruited patients and the relative information will be checked. Moreover, at each follow up visit the physician will need to check the consistency of patient CRF.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on during months 1 – 30 of the project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 29.000

List of activities envisaged under the Operational Objective:
Activity no. 2.1 - Name: **Pain intensity assessment** *- Cost: euro* ***14.000***

Activity no. 2.2 - Name: **Pain treatment** *- Cost: euro* ***15.000***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 2.1 - Name: Pain intensity assessment
Explain the individual activity
Physicians (AOUC) will visit at least 170 patients and perform the relative measurements.
Activity no. 2.2 - Name: Pain treatment
Explain the individual activity
Physicians (AOUC) will visit at least 170 patients and perform the relative treatments.

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities
VAS scale
BPI questionnaire
All information will be recorded in an individual Case Report Form (CRF) for each patient.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*

Dr Firenzuoli 1
Dr Mediati 1
Dr Sivelli 1

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*

Physician 12 ftpm

- *Total Personnel (full time person month) 15* ftpm

Subcontracts:[4]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

The power of the study is calculated for pain relief analysis considered as a continuous variable (variation of the VAS score) outcome, assuming that the 60% of patients treated with cannabis decreases from mean VAS=6.5 to mean VAS=3.5 and the remaining 40% has no pain relief as well as the not-treated group (data not published, Mediati RD, 2018).

[4] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

Timing:
Indicate the months during which the Activity will be carried out.

Months 1 – 30: activity 2.1 and activity 2.2 up to the 30th month (see Gantt flowchart).

Operational Objective no. (3)
Name: Galenic formulations of Cannabis
Description of the operational objective:
Preparation of the drug treatment (oil extraction of cannabis) and placebo. Chemical characterization of the oil preparations.

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)
If yes, please indicate in which activity(ies):

Evaluation of galenic preparation

X the objective includes check points (*milestones*)
If yes, please indicate in which activity(ies):

Each three months chemical analyses of the oil preparation will be performed.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on in the 1 - 30 months of the project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 64.000

List of activities envisaged under the Operational Objective:
Activity no. 3.1 - Name: **Olive oil (Ph. Eur.) extraction of female Cannabis inflorescence and placebo provided**
- Cost: euro ***60.000***
Activity no. 3.2 - Name: **Cannabinoid determination in oil extract by HPLC/DAD**

- Cost: euro ***4.000***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 3.1 - Name: Olive oil (FU) extraction of female Cannabis inflorescence
Explain the individual activity
The preparation of Cannabis oil is an oil extraction at the ratio 1 g: 10 mL. Commercial placebo cannabis will be provided.

Activity no. 3.2 - Name: Cannabinoid determination in oil extract by HPLC/DAD
Cannabidiol (CBD), Cannabinol (CBN), Δ-9-tetrahydrocannabinol (THC), Δ-9-tetrahydrocannabinoic acid (THCA) and myrcene concentration in galenic oil preparations of cannabis will be determined.

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities

- Dry stove
- Turbo-emulsifier
- Water bath
- Vacuum pump
- HPLC-DAD (Thermo-Fisher Surveyor Plus) equipped with quaternary pump, autosampler and UV DAD;
- Poroshell® 120 SB-C18 column (2.1 x 150 mm 2.7 micron) with pre-column.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*
Dr Ruffino 2 ftpm

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*
Fellowship 12 ftpm
- *Total Personnel (full time person month)* 14 ftpm

Subcontracts:[5]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

Cannabis/placebo oil will be prepared for each patient for a 6-month treatment. Chemical analyses of the oil will be carried out.

Timing:
Indicate the months during which the Activity will be carried out.

Months 1 – 30: activity 3.1 up to first 30 months and activity 3.2 every 3 months (see Gantt flowchart).

[5] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

Operational Objective no. (4)
Name: Pharmacokinetic evaluations
Description of the operational objective:
Patients will give their informed written consent to the project and agree to undergo blood sampling and pharmacokinetic analyses**:** Cannabidiol (CBD), Cannabinol (CBN), Δ-9-tetrahydrocannabinol (THC), Δ-9-tetrahydrocannabinoic acid (THCA) and 11-hydroTHC concentration in blood samples will be determined by liquid chromatography tandem mass spectrometry (LC-MS/MS).

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)

If yes, please indicate in which activity(ies):

At least 40 blood samples from 40 patients should be recruited and the relative pharmacokinetic analyses performed (see above).

X the objective includes check points (*milestones*)

If yes, please indicate in which activity(ies):

Each six months the number, quality and results of pharmacokinetic analyses will be checked.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on in 1-16 months of the project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 8.000

List of activities envisaged under the Operational Objective:
Activity no. 4.1 - Name: **Blood sample collection** *- Cost: euro* ***1.000***
Activity no. 4.2 - Name: **Cannabinoid determination in blood samples by LC-MS/MS**

- Cost: euro ***7.000***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 4.1 - Name: Blood sample collection
Explain the individual activity

Physicians (AOUC) will collect blood sample during the follow up visit T1
Activity no. 4.2 - Name: Cannabinoid determination in blood samples by LC-MS/MS
Explain the individual activity
Cannabidiol (CBD), Cannabinol (CBN), Δ-9-tetrahydrocannabinol (THC), Δ-9-tetrahydrocannabinoic acid (THCA) and 11-hydroTHC concentration in blood samples will be determined.

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities
Written informed consent will be requested to each patient.

- 4000 Q trap system (ABsciex) constituted by HUPLC Ultimate3000 (Thermofisher), and a hybrid triple quadrupole linear ion trap MS;
- Poroshell® 120 SB-C18 column (2.1 x 150 mm 2.7 micron) with pre-column.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*
Dr Baronti 2 ftpm

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*

- *Total Personnel (full time person month)* 2 ftpm

Subcontracts:[6]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

Cannabidiol (CBD), Cannabinol (CBN), Δ-9-tetrahydrocannabinol (THC), Δ-9-tetrahydrocannabinoic acid (THCA) and 11-hydroTHC concentration in blood samples will be determined by liquid chromatography tandem mass spectrometry (LC-MS/MS). Each six months the number, quality and results of pharmacokinetic analyses will be checked.

Timing:
Indicate the months during which the Activity will be carried out.

Months 1 – 16: activity 4.1 up tp first 6 months and activity 4.2 from 5 to 16th month (see Gantt flowchart).

Operational Objective no. (5)
Name: Follow up
Description of the operational objective:
Each patient will be subjected to a baseline visit (T0), which will correspond to the selection visit to

6 For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

verify the inclusion and exclusion criteria of the protocol and to the following subsequent follow up visits:
T1: 7 days
T2: 14 days
T3: 30 days
T4: 3 months
T5: 6 months
T6: 1 year

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)
If yes, please indicate in which activity(ies):

At least 170 patients should be visited at T0-T1-T2-T3-T4-T5-T6 to reach the power of the study (see above).

X the objective includes check points (*milestones*)
If yes, please indicate in which activity(ies):

Each six months the number of followed up patients will be checked.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on in the 1-30 months of the project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 44.000

List of activities envisaged under the Operational Objective:
Activity no. 5.1 - Name: **Clinical visit at T0***- Cost: euro* ***12.000***
Activity no. 5.2 - Name: **Clinical visits from T1 to T6** *- Cost: euro* ***32.000***
For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 5.1 - Name: Clinical visit at T0
Explain the individual activity
Each patient will be subjected to a baseline visit (T0), which will correspond to the selection visit to verify the inclusion and exclusion criteria of the protocol.

Activity no. 5.2 - Name: Clinical visits from T1 to T6
Explain the individual activity
Each patient will be subjected to the subsequent follow up visits:
T1: 7 days
T2: 14 days
T3: 30 days
T4: 3 months
T5: 6 months
T6: 1 year

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities
BPI questionnaire
All information will be recorded in an individual Case Report Form (CRF) for each patient.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*

Dr Firenzuoli 1
Dr Mediati 1
Dr Sivelli 1

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*

Trained Monitor 5 ftpm
Physician 24 ftpm

- *Total Personnel (full time person month)* 32 ftpm

Subcontracts:[7]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.
Principal Investigator will contact a notary for the ATS legal constitution.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

Present study has 90% power to detect a minimum difference of VAS=1 in pain relief between study arm 1 and arm 2 (with at least 85 recruited patients/each arm), assuming α= 0.05 and a 20% correlation between group pre-intervention and post-intervention, with co-variance analysis comparing final mean values of the two studied groups adjusted for the baseline values. Each six months the number of followed up patients will be checked.

Timing:

[7] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

Indicate the months during which the Activity will be carried out.

Months 1 – 30: activity 5 and activity 5.2 up to the 30th month (see Gantt flowchart).

Operational Objective no. (6)
Name: Pharmacovigilance
Description of the operational objective:
Investigators will be responsible for monitoring the safety of patients who enter this study

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)

If yes, please indicate in which activity(ies):

At least 170 patients should be recruited and the relative AEs onset monitored and recorded (see above).

X the objective includes check points (*milestones*)

If yes, please indicate in which activity(ies):

Each six months the number of AEs will be checked. All SAEs will be reported to the Pharmacovigilance responsible person within 24 hours of the Investigator's knowledge of the event.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on during the entire project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 29.000

List of activities envisaged under the Operational Objective:
Activity no. 6.1 - Name: **Safety assessment** *- Cost: euro* ***15.000***
Activity no. 6.2 - Name: **AEs evaluation** *- Cost: euro* ***4.000***
Activity no. 6.3 - Name: **AEs Reporting** *- Cost: euro* ***10.000***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 6.1 - Name: Safety assessment
Explain the individual activity
Investigators will be responsible for monitoring the safety of patients who enter this study
Activity no. 6.2 - Name: AEs evaluation
Explain the individual activity
A qualified Investigator will evaluate all adverse events as to: intensity, causality, duration, action taken, outcome.
Activity no. 6.3 - Name: AEs Reporting
Pharmacovigilance responsible person will inform relevant Regulatory Authorities and Ethics Committees of all relevant information.

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities
Equipments available include a mainframe, and personal computers for data storing, analysis as well as word processing; plus any other standard facilities for conducting and developing the activities.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*

Research fellow 12 ftpm
Dr Vannacci 1
Dr Lombardi 2

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*

- *Total Personnel (full time person month)* 15 ftpm

Subcontracts:[8]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

The Investigator will report the action taken with treatment because of an AE or SAE, as applicable (e.g., discontinuation or reduction of drugs, as appropriate) and report if concomitant and/or additional treatments were given for the event.

Timing:
Indicate the months during which the Activity will be carried out.

Months 1 – 36: activity 6.1, 6.2 and 6.3 for the entire project (see Gantt flowchart).

Operational Objective no. (7)
Name: Phytovigilance

[8] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

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Description of the operational objective:
Within the Phytovigilance system for Cannabis ARs, coordinated by the Italian National Institute of Health, will be collect and evaluated the spontaneous reports of ARs occurred after the assumption/administration of cannabis preparations.

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)
If yes, please indicate in which activity(ies):

At least 170 patients should be recruited and the relative ARs onset monitored and recorded (see above).

X the objective includes check points (*milestones*)
If yes, please indicate in which activity(ies):

Each six months the number of ARs will be checked.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on during the entire project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 2.500

List of activities envisaged under the Operational Objective:
Activity no. 7.1 - Name: **Cannabis Adverse Reactions (ARs) collection** - *Cost: euro* ***1.500***
Activity no. 7.2 - Name: **Cannabis ARs evaluation**- *Cost: euro* ***1.000***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 7.1 - Name: Cannabis Adverse Reactions (ARs) collection
Explain the individual activity
The spontaneous reports of ARs occurred after the assumption/administration of cannabis preparations will be collected in the Phytovigilance system, coordinated by the Italian National Institute of Health.
Activity no. 7.2 - Name: Cannabis ARs evaluation
Explain the individual activity

The spontaneous reports of ARs, occurred after the assumption/administration of cannabis preparations, will be evaluated once inserted in the specific Phytovigilance system.

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities
All information will be recorded in an individual Case Report Form (CRF) for each patient.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*

Dr Vannacci 1
Dr Lombardi 2

R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)

- *Total Personnel (full time person month)* 3 ftpm

This OO will be performed in collaboration with ISS (external research organization).

Subcontracts:[9]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

A Scientific Committee, including experts in toxicology, pharmacology, pharmacognosy, phytotherapy, botany, pediatrics, homeopathy, has been appointed for the evaluation of the reports and the detection of risk signals. A Steering Committee with experts in pharmacovigilance, pharmacoepidemiology and regulatory aspects supports the activities of the Scientific Committee.

Timing:
Indicate the months during which the Activity will be carried out.

Months 1 – 36: activity 7.1 and 7.2 for the entire project (see Gantt flowchart).

Operational Objective no. (8)
Name: Data analysis
Description of the operational objective:
During the period of recruitment, patients' data will be collected by a monitor and will be input into a dedicated database for the statistical analysis.

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables

[9] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)

If yes, please indicate in which activity(ies):

Data of at least 170 patients should be available and analysed (see above).

X the objective includes check points (*milestones*)

If yes, please indicate in which activity(ies):

Each six months the quality of patient data available in the database will be checked.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on during 13-33 months of the project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 19.500

List of activities envisaged under the Operational Objective:
Activity no. 8.1 - Name: **Data entry** *- Cost: euro* ***15.000***
Activity no. 8.2 - Name: **Statistical Data Analysis** *- Cost: euro* ***4.500***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 8.1 - Name: Data entry
Explain the individual activity
During the period of recruitment, patients' data will be collected by a monitor and will be input into a dedicated database.
Activity no. 8.2 - Name: Statistical Data Analysis
Explain the individual activity
Data analysis will be conducted starting from the end of the last patient follow up (from month 30 of the project).

Tools/equipment:
Define the tools and equipment that will be used to carry out the activities
Dedicated database.
Equipments available include a mainframe, and personal computers for data storing, analysis as well as word processing; plus any other standard facilities for conducting and developing the activities.

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*
Dr Bonaiuti 4

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*
Fellowship 12 ftpm

- *Total Personnel (full time person month)* 16 ftpm

Subcontracts:[10]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.
Principal Investigator will contact a notary for the ATS legal constitution.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

Present study has 90% power to detect a minimum difference of VAS=1 in pain relief between study arm 1 and arm 2 (with at least 85 recruited patients/each arm), assuming α= 0.05 and a 20% correlation between group pre-intervention and post-intervention, with co-variance analysis comparing final mean values of the two studied groups adjusted for the baseline values.

Timing:
Indicate the months during which the Activity will be carried out.

Months 13 – 33: activity 8.1 from 13 to 30th month and activity 8.2 from25 to 33th month.

(see Gantt flowchart)

Operational Objective no. (9)
Name: Study results
Description of the operational objective:
All participants will discuss the results of the study in several scientific meeting planned during the project. A final scientific report will be prepared and approved by all partners. Dissemination of study results will happened through congress and articles in international journals.

Expected Results: deliverables e milestones
Explain the expected results during the operational objective, including whether specific deliverables and milestones are foreseen for the implementation of the project.

X specific measurable and verifiable results will be produced during the course of the objective (*deliverables*)

[10] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

If yes, please indicate in which activity(ies):

Study results will be discussed to produce a final report and abstract and articles for international journals.

X the objective includes check points (*milestones*)
If yes, please indicate in which activity(ies):

Scientific dissemination will be monitored by the Principal Investigator.

The milestones and deliverables must be highlighted in a specific GANTT diagram (see Annex B1)
The specific activities must describe the project check points (milestones), and describe the main measurable and verifiable results (deliverables) specifying the expected values at the end of the project.

Timing:
Indicate the months during which the Operational Objective will be achieved.

This operational objective will be carried on during 25-36 months of the project.

Total cost of the objective:
Indicate the total cost of the Operational Objective

Euro 33.250

List of activities envisaged under the Operational Objective:
Activity no. 9.1 - Name: **Discussion of the results** *- Cost: euro* ***20.000***
Activity no. 9.2 - Name: **Study final report and dissemination** *- Cost: euro* ***13.250***

For each activity, provide the required information:
Activities must be numbered with reference to the relative Operational Objective (e.g.: Activities under Operational Objective 1 must be numbered 1.1,1.2,1.3, etc.).
It is necessary to repeat the activity sheet for each activity that makes up the Operational Objective.

Activity no. 9.1 - Name: Discussion of the results
Explain the individual activity
Principal Investigator will take care to organize one meeting with all the participants working on the research every six months of the projects
Activity no. 9.2 - Name: Study final report and dissemination
Explain the individual activity
According to the ICH-GCP, the Principal Investigator will undertake to produce a report on the study, publish all the data collected as described in the Protocol and to ensure that the data are reported responsibly and consistently.
Tools/equipment:
Define the tools and equipment that will be used to carry out the activities

Human resources:
Specify for each partner the skills and relative timing (in full time person month) needed to carry out the activities.

- *Staffes personnel (full time person month)*

Dr Firenzuoli 1

Dr Mediati 1
Dr Becorpi 1
Dr Angiolini 1
Dr Meattini 1
Dr Catarzi 1
Prof Vannacci 1
Dr Ruffino 1
Dr Baronti 1

- *R&D personnel with fixed-term employment relationships specifically hired for the project (full time person month)*

- *Total Personnel (full time person month)* 9 ftpm

Subcontracts:[11]
Identify the possible need to acquire specific technical skills or patents for carrying out the activities.

Expected results: Deliverables and/or Milestones
Describe the project results check points (milestones) and describe the main measurable and verifiable results (deliverables) indicated in the "operational objective" section, specifying the units of measurement and expected values at the end of the project.

Five scientific meetings to discuss the results, a final report of the study, abstract for international congresses and several scientic publications in international journals will be produced.

Timing:
Indicate the months during which the Activity will be carried out.

Months 25 – 36: activity 9.1 from 25 to 36th month and activity 9.2 from 34 to the 36th month.

(see Gantt flowchart)

Total cost of the Operational Objectives

OO1 - Cost: **107.000** euro
OO2 - Cost: **29.000** euro
OO3 - Cost: **64.000** euro
OO4 - Cost: **8.000** euro
OO5 - Cost: **44.000** euro
OO6 - Cost: **29.000** euro
OO7 - Cost: **2.500** euro
OO8 - Cost: **19.500** euro
OO9 - Cost: **33.250** euro

Total Overheads – Cost: **13.750** euro

Total project cost – Cost: **350.000** euro

Total full time person month

[11] For public bodies, at this stage, it is sufficient to indicate the type of service required, since the subcontractor will have to be identified in the manner provided for by the regulations in force on the subject..

- *Staffes personnel (full time person month)*

Dr Firenzuoli 4
Dr Mediati 4
Dr Sivelli 3
Dr Becorpi 3
Dr Angiolini 3
Dr Meattini 3
Dr Catarzi 1
Dr Picozzi 1
Dr Ruffino 3
Dr Baronti 3
Dr Vannacci 3
Dr Lombardi 4
Dr Bonaiuti 4

- *R&D personnel*

Physician 36
Trained monitor 36
Research Fellow 12
Fellowships 24 (2 x 12)

Total personnel: **147** full time person month

Description of the activity carried out by the External Research Organization participating in the project pursuant to art. 4 of the call for proposals, specifying whether the participating ROs carry out an additional activity or whether they contribute to the activities listed above.

The University of Texas - MD Anderson Cancer Center (Houston, TX) - Prof Lorenzo Cohen, Director of the Integrative Medicine Program, will be involved in the discussion of the study results to compare our conclusions with the clinical practice of MD Anderson Institute for the management of chronic pain (see OO9).

Description of the activity carried out by the RO participating in the project pursuant to art. 4 of the call for proposals, specifying whether the participating ROs carry out an additional activity or whether they contribute to the activities listed above.

Istituto Superiore di Sanità (Roma, Italy) - Centro Nazionale per la Ricerca e la Valutazione preclinica e clinica dei Farmaci - Dr Francesca Menniti Ippolito, Dr Roberto Da Cas and Dr Marco Massari will be involved in the Phytovigilance assessment and Data analysis (see OO7 and 8).

The project includes clinical trial phases

- ***Yes***

If YES specify:

type of study placebo-controlled randomized prospective multicenter
trial phase (if applicable) 3

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If the project provides for the start-up of activities, clinical trial phases must be submitted to the relevant ethics committee for a positive opinion when the agreement is signed

The project includes animal testing phases:

- **NO**

If the project involves animal testing phases, it is necessary to submit, at the conclusion of the agreement, the authorization of the Italian Ministry of Health according to art. 31 of Decreto Legislativo 26 del 4/3/2014.

SECTION 4 – PROJECT SPECIFICATIONS IN RELATION TO THE SELECTION CRITERIA

A) Scientific and technical quality of the proposal

Describe:

- *scientific novelty, scientific merit and quality of approach;*
- *scientific evidence and credibility of the proposal;*

Modern medicine have made it possible to identify real herbal medicines, distinct from herbal products and simple herbs. **Phytotherapic medicines** are all those medicines whose active ingredient is a plant substance. These medicines have been officially approved by AIFA, which has verified their quality, efficacy and safety, and are sold exclusively in pharmacies, some on prescription and others as non-prescription medicines or over-the-counter medicines (Ministero della Salute, Fitoterapici 2013).

In many other cases, medicinal plants can be used in the form of medicinal galenic preparations, provided by the Ministry itself (Firenzuoli *et al.,* 2005). For example: *Zingiber officinale* extract for Nausea and vomit, *Mentha piperita* essential oil for Irritable bowel syndrome, and so on *Cannabis sativa* (and other botanical species).

Recently we can use the medicinal herbs also for cancer patients, to mitigate numerous symptoms related to conventional therapies used in cancer patients, like the use of infusions to improve digestion, reduce nausea, anxiety, insomnia or constipation, and to control the oncological pain. On the other hand, the Clinical phytotherapy has been present for over twenty years in the Health Plans of the Tuscany region of Italy. The most studied vegetal substances are *Cannabis sativa* to control pain in cancer patients, and side effects of opioids. Thus, it is pivotal that the clinical efficacy

and safety of herbal drugs is demonstrated by rigorous clinical phase II and III clinical trials like the study here presented.

- *clarity and appropriateness of the project development strategy;*

Medicinal herbs are natural products and their chemical composition varies depending on several factors, such as botanical species, used chemotypes, the anatomical part of the plant used (seed, flower, root, leaf, and so on) and also storage, sun, humidity, type of ground, time of harvest, geographic area. Merchandized products containing on the label the same product vary in their content and concentrations of chemical constituents from batch to batch; and even the same manufacturer can merchandize in different period's products containing different substances although standardized to achieve a high pharmaceutical quality. This variability can result in significant differences in pharmacological activity: involving both pharmacodynamic and pharmacokinetic issues.

The appropriateness of the present project is assured by the use of Cannabis FM2. In fact, The quality and chemical definition of the **Cannabis FM2** produced by SCFM of Florence are certified by the Ministry of Health's documentation. The work of pharmacodynamics and pharmacokinetics are described and documented by the research conducted at the Istituto Superiore di Sanità, and the Cannabis FM2 can be used in the form of galenic preparations, herbal medicines, provided by the Ministry of Health. In particular, the Ministry of Health and the Ministry of Defense presented and signed a collaboration agreement on 18 September 2014 for the launch of the pilot project for the national production of substances and preparations of vegetable origin based on cannabis (Ministero della Salute, Il progetto pilota per la produzione nazionale di Cannabis, 2018). It is fundamental to ensure unity in the safe use of masterly preparations of plant-based substances based on cannabis and to avoid the use of unauthorized, counterfeited or illegal products. The national industrial production of these phytotherapics that have come to fruition will allow access to these therapies at an appropriate cost. The collaboration agreement between the Ministers of Health and Defense has been realized with the participation of many institutional bodies that have worked for two years for the success of the project. Within the framework of an ad hoc working group, all the steps necessary to start the national production of medical cannabis have been identified.
In September 2016, the research and development phase of the pilot project was successfully completed and the first batches of active substance of vegetable origin based on dried and milled cannabis, called Cannabis FM2, to be produced according to the requests of the Regions and available, are available. Public administrations. These lots are issued by the SCFM of Florence in accordance with the Community directives on medicinal products and pharmacologically active substances authorized for distribution by the State Cannabis Authority, which performs its functions at the Ministry of Health, as required by Ministerial Decree 9 / 11/2015.
This is the product Cannabis FM2 (containing THC 5% - 8% and CBD 7.5% - 12%), the first active substance based on cannabis produced in accordance with European directives on medicines (EU - GMP).

Also, the study design is rigorous and the power of the study with the relative needed sample size has been assessed to be able to describe also the minimum variation of the studied outcome (i.e. pain variation equal to a VAS score = 1).

- *applicability and transferability of results.*

Evidence-based public health requires that health care decisions should be based on the best evidence available (Wang et al., 2005). To determine the effectiveness of a public health intervention in a specific setting, a well-designed and well-conducted randomized controlled trial

(RCT) may provide the best evidence (Rychetnik et al., 2002).

Our study aimed to explore the evidence able to determining whether Cannabis, effective in other settings (e.g. other types of cancer pain, different cancer patients,..), can be of potential use to treat another kind of cancer chronic pain (i.e. pain induced by aromatase inhibitors). The transferability of study results is just provided by an accurate RCT.

B) Level of innovation:

Describe the degree of innovation of the project in terms of

- *product innovation;*
- *process innovation;*
- *new procedures, standards and protocols.*

The clinical **phytotherapy** refers to the medical discipline that uses medicinal plants and derivatives in the prevention and treatment of diseases, with regard to the pharmacological properties of the chemical constituents present in the plant, or better in the used preparation. In reality, in every country, traditional medicines find foundation in magical or religious beliefs, or popular experience. Moreover, the World Health Organization is engaged to establish guidelines for methodology of clinical research and the appraisal of effectiveness of traditional medicine. However, the modern and scientific phytotherapy does not follow particular philosophies or religious beliefs, nor diagnostic or therapeutic methods other than those of scientific medicine if anything requires and imposes a scientific verification of the knowledge entrusted to us by tradition (Firenzuoli et al., 2007). In fact, the medicinal plants can simply be considered a container of chemical substances, sometimes isolated and used as such in therapy. In other cases, they can be a source of raw material for the production of hemi-synthetic drugs, or as a basis for the production of real phytotherapic drugs. For example, in the case of Hypericum (St. John's wort) also the clinical ad pharmacological studies have shown that the best antidepressant activity is explained by the phytotherapic extract due to the simultaneous presence of the group of flavonoids, hypericin and hyperforin.

In contrast to the popularity of herbal medicinal products, physicians can have a critical view of them. Besides dogmatic obstacles, this is based on the frequently missing clinical trials that clearly demonstrate their effectiveness. Moreover, the studies are very heterogeneous, and results vary greatly preventing consistency in clinical practice. There is therefore a lost opportunity to improve phytotherapy practice, because the work being done cannot represent a body of data on which to base clear clinical recommendations. Then, it is mandatory that the clinical efficacy and safety of herbal drugs is demonstrated by double-blind, placebo-controlled and drug-based trials.

Then, the innovation of the present project is represented by the importance of a new clinical protocol investigating intringuing galenic preparations of Cannabis. In this context, the planned procedures design a rigorous research line able to offer new healthcare approaches to the treatment of oncologic chronic pain and novel guidelines in **evidence-based phytotherapy** and **integrative oncology**.

C) Reliability of applicants:

Describe the reliability of the applicants in terms of their reliability:

- *experience already gained in carrying out similar projects;*
- *technical and scientific qualification (adequacy and complementarity of the competences involved) of the research groups with particular reference to the project proposal;*
- *Facilities, equipment and resources available for the project;*
- *connection with national and international research and development networks.*

The CERFIT, reference structure for the Phytotherapy of the Tuscany Region, has distinguished itself over time as a reference point for research on the efficacy and safety of phytotherapics, control of adverse reactions and phytovigilance. Moreover, it has contributed to the birth of the relative national center at the Istituto Superiore di Sanità, and to the working group on Cannabis in the ministerial settings. Other specific activities are those related to clinical assistance, to research and training, in addition to specific activities carried out in collaboration with other regional reference structures of complementary medicines and the Tuscan Network of Integrated Medicine. We have institutional collaborations with:

a) the Ministry of Health (an integral part of the **Ministry's Cannabis Working Group**);
b) the **Istituto Superiore di Sanità** for the control and analysis of adverse reactions to natural products and cannabis;
c) various hospital and university facilities for research purposes that have also produced numerous scientific publications, such as:
Department of Biology of the University of Florence (Prof. Renato Fani) for research on the activity of endophytes and essential oils;
Department NEUROFARBA of the University of Florence (Prof. Alfredo Vannacci and Prof. Carla Ghelardini) for phytovigilance research and pharmacology on herbal extracts;
Department of Experimental and Clinical Medicine University of Florence (Prof. Francesco Sofi) for specific training;
Department of Pharmacy of the University of Pisa (Prof. Luisa Pistelli) for phytochemical research;
Department of Pharmacology of the University of Messina (Prof. Gioacchino Calapai) for pharmacological research;
d) international collaborators: Prof. Lorenzo Cohen, Director of Integrative Medicine of **MD Anderson Cancer Center** of Houston (Texas, USA); Prof. Barrie Cassileth (**Memorial Sloan Kettering Cancer Center** of New York) and Prof Stefan Willich (**University Charitè** of Berlin) for Research and Educational Programs in Integrative Medicine

Recently the AOU Careggi has formally established the **CERFIT** as

- a **Research and Innovation Center in Phytotherapy and Integrated Medicine**, characterized by the presence of welfare activities, research and advanced training, as well as having the ability to transfer the results of the most innovative translational research in the biomedical field, scientific and assistance reference for the health service structures and the stakeholders to the assistance and organizational practice.

The Center's activities have always been concentrated in collaborations with the **Regional Reference Structure for Complementary Medicines** (MC), and with the **Tuscany Network of Integrated Medicine** (RTMI) (Dott.ssa Sonia Baccetti, Azienda USL Toscana Centro), currently called "Regional Center of Integrated Medicine" and specific activities related to the single Phytotherapy discipline.
The activities carried out at the regional level are mainly related to the work of the envisaged Commissions (e.g. Training) or working groups for Integrated Oncology (identification of therapeutic protocols) and for pain control, as well as for the planning of Medicine activities. complementary to the Vasta Area, as well as collaborations with the Tuscan Universities for the purpose of disseminating MC training in university study courses and increasing research in the sector.
Our scientific production can be verified in all published research in PubMed and described in Annex CV.

Fabio Firenzuoli is:

- Teacher of Clinical phytotherapy and phytovigilance at the University of Florence, School of Medicine, Scientific coordinator of Master in General and clinical Phytotherapy (University of Florence)
- Member of Editorial Board of Phytomedicine
- Peer reviewer for several scientific journal
- Lead Guest Editor of the Special Issue "Essential oils" Evidence Based Complementary and Alternative Medicine, Hindawi Ed., 2013
- Guest editor of Special Issues "The European Heritage of Folk Medicines and Medicinal Foods: Its Contribution to the CAMS of Tomorrow" Evidence Based Complementary and Alternative Medicine, Hindawi Ed., 2012
- Editor "European Traditional Medicine" Evidence-Based Complementary and Alternative Medicine, Supplement, 2007
- Editor HERBAL MEDICINES AND CANCER, Suppl. Minerva Medica Ed., Florence, 2001

Author of several books and scientific publications in journals and books in Italian and English language, in the fields of Herbal medicine, Phytotherapy, and Phytovigilance:

- CANNABIS. “ERBA” MEDICA. Edra Edizioni, Milano, 2015
- CANNABIS … per tutti LSWR Ed.,Milano, 2015
- ERBE ANTI CANCRO. LSWR Ed, Milano, 2018
- LE INSIDIE … del Naturale. LSWR Ed, Milano, 2017
- INTERAZIONI TRA ERBE, ALIMENTI E FARMACI, II^ ed. Tecniche Nuove, Milano, 2009
- FITOTERAPIA, IV^ ed. Masson - Elsevier Ed., Milano, 2009

His collaborators have adequate and documented knowledge and expertise at clinical, biological, chemical, epidemiological, biostatistical, pharmacological and computational level. Another guarantee for feasibility of this project derives from the fact that the hosting institute has technical and scientific resources to conduct project, including data management and analysis, as well as manuscript preparation. Equipment available in the Institute includes a mainframe, and personal computers for data storing, analysis as well as word processing; plus any other standard facilities for conducting and developing the project.

Hosting Institute will make use of several essential collaborations to achieve **TosCannabis** goals:

AOU Careggi
The Collaborators for patient recruitment are already cooperating in the clinical setting of the hospital and all participants are well integrated and used to collaborate successfully. In particular, several physicians (Palliative care and clinic of Pain, Phytotherapy Unit and others) already use the galenic preparations of cannabis from 4 years in their clinical practice according to regional indications.

University of Florence
The Pharmacovigilance and Pharmacoepidemiology Unit of Florence University (NeuroFarBa Department) has a long-standing expertise in efficacy and safety evaluation of drugs and vaccines. The group is part of regulatory task forces on drugs and vaccines adverse events evaluation of Tuscan Region and Italian Medicines Agency (AIFA). The Unit coordinated and participated to several national and international projects of spontaneous and active pharmacovigilance and pharmacoepidemiology studies on drugs and vaccines. Furthermore, through its Information and Communication Technology activity (now formalized in the joint laboratory “Scarab Lab”), the Unit contributed to the design of devices and distributed systems to early detect risks and problems related to vaccines, drug therapies and natural products in order to improve patient safety, wellness and treatment adherence. NeuroFarBa Pharmacology Unit is responsible for data collection, treatment

and analysis of adverse reactions to drugs and vaccines for the healthcare system of Tuscany County.

Project Scientific Leader, **Alfredo Vannacci** (M) MD, PhD**,** is associate professor in Pharmacology at Florence University. His research expertise and interests include pharmacology, medical toxicology, pharmacovigilance, pharmacoepidemiology, drugs and vaccines effectiveness and safety. He has published many scientific articles on the mentioned subjects on many important peer reviewed international journals. He is the chief of the University of Florence Unit of the Tuscan County Phamacovigilance Centre. He is head of the Unit of Adverse Drug Reactions Monitoring and Pharmacoepidemiology and member of the Unit of Pediatric Pharmacology of the University of Florence. He is a long-standing collaborator of the project Principal Investigator, Dr Fabio Firenzuoli as evidenced from many national and international publications.

ISPRO
"Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment", this is the final definition identifies by NCI (Witt et al., 2017). In Tuscany, the regional oncological network (ISPRO) collaborates with the Center for the Integrative Medicine on the theme of integrative oncology. ISPRO has also co-organized the major European Congress in Integrative Oncology (Firenze, 2018).

Azienda USL TOSCANA CENTRO
The local Galenic laboratory (preparing Cannabis oil for the project) performs the task of packaging tetrahydrocannabinoid preparations to be used in the curative treatment of secondary spasticity related to neurological diseases and in particular to multiple sclerosis, chronic neuropathic pain, cancer pain, nausea and vomiting caused by chemotherapy and it is the landmark of the Regional Health Service. The preparation of cannabis-based formulations for therapeutic use that takes place in the laboratory consists of six levels of control and continuous monitoring to ensure the highest quality of the preparations and safety possible for patients.

The local laboratory of Clinical Toxicology (providing the biological and chemical analyses for the project) performs a wide range of drug-toxicological analyses on various biological matrices (blood, urine, hair) and non-biological matrices (food supplements, drugs, drugs), to answer the clinical and medico-legal questions of institutional clients (hospital departments, services for drug addicts, alcohol centers) and private customers. The high automation of screening analysis allows processing a large number of samples and allows operators to pay particular attention to the quality of the analytical data. The advanced instrumental equipment, the qualification of the personnel and the accreditation of the tests allow the laboratory to perform second level toxicological analyses (confirmations) and analysis in contradictory (counter-analysis).

National and international research cooperative network will be established between all project partners and the two external organizations, **Istituto Superiore di Sanità** and **The University of Texas, MD Anderson Cancer Center.**

D) Technical validity and economic viability of the project:
Describe:

- *Technical validity: analysis of the innovativeness with regards to the technical and scientific aspects of the proposal (to be evaluated also on the basis of appropriate international parameters) and verification of their feasibility;*

Evidence-based public health requires that health care decisions should be based on the best evidence available (Wang et al., 2005). To determine the effectiveness of a public health intervention in a specific setting, a well-designed and well-conducted randomized controlled trial (RCT) may provide the best evidence (Rychetnik et al., 2002).

- *Economic viability: consistency between costs and expected results*

Personnel cost

People taken on board during the project will be full time dedicated to the study and have a salary estimated by usual contracts of the hosting institutions.

Drug cost
Galenic laboratory of Santa Maria Nuova Hospital has estimated the cost for 45 ml of Cannabis oil for patient/month.

Patient cost (insurance)
Mean cost of a clinical phase III trial insurance has been considered.

Ethical requirements cost
These costs are estimated and available by the Ethical Committee of the hosting institution.

Biological and chemical analyses cost
Clinical Toxicology laboratory has produced a punctual estimation of the costs to conduct pharmacokinetic analyses and to analyze all the batchs of Cannabis oil.

- *sustainability*

Evaluation of both the clinical and implementation components of the study will allow sustainability in the study sites and further scale-up. Thus, the average cost per patient will be estimated at each of the study centres, pre- and post-intervention. Moreover, we believe that our project is sustainable since (based on NHS Quality Improvement Sustainability Model):

- there are some obvious and supported by evidence benefits beyond helping patients such as reducing waste and making staff jobs easier;
- there is a system in place to provide evidence of impact, including benefits analysis, monitor progress and communicate the results;
- staff is confident and competent in the way of working and new personnel will be specifically trained;
- Principal Investigator and clinicians are highly involved and visible in its support of the project;
- project goals are clear and have been shared widely, they are consistent with and support the hosting organisations' strategic aims for improvement;
- hosting organisations have demonstrated successful sustainability of improvements before and has a 'can do' culture;
- facilities and equipment are all appropriate to sustain the project.

E) Ability of the project to create good network relationships:
Describe the project's ability to create good network relationships through:
sharing and exploitation of technological infrastructures, such as integrated organisational and research platforms (also with Clusters identified by the Tuscany Region and regional networks)

The present proposal aims to build a strongly multidisciplinary research core group able to break the boundaries and bridge together two main tasks: the treatment of oncological chronic pain and the complementary and integrative medicine. In fact, the general objective of the present proposal is to contribute in promoting the creation of a synergic cluster of excellence dedicated to the pharmacological exploitation of Cannabis galenic preparations for resistant cancer pain. The synergy of researchers from different fields (oncology, ginecology, pharmacology, toxicology, chemistry, pharmacy and epidemiology) with experts in clinical phytotherapy can lead to the development of integrative pain treatment.

Specifically, the project is carried out with several oncological structures (AOUC) and in partnership with two Tuscany Research Organization:

- ISPRO, organization of the Regional Health Service, having the operative coordination of the Tuscan oncology network. Tuscany oncology network coordinates every prevention, diagnosis, treatment and research activities carried out in all Tuscan health service and in the same ISPRO. The purpose of ISPRO is to promote measure and study primary, secondary and tertiary cancer prevention and to organize and coordinate, in synergy with the regional health services, the diagnosis, treatment and rehabilitation courses, as well as research programs in oncology.

- University of Florence with the Pharmacovigilance and Pharmacoepidemiology Unit of NeuroFarBa Department having a long-standing expertise in efficacy and safety evaluation of drugs and vaccines. The group is part of regulatory task forces on drugs and vaccines adverse events evaluation of Tuscan Region and Italian Medicines Agency (AIFA).

- Azienda USL Toscana Centro with the Clinical Toxicology Laboratory (accredited by the Ministry of Health) to whom the Tuscany Region has conferred the competence on all the regional territory according to the law 376/2000 and the Galenic Laboratory of Santa Maria Nuova Hospital (excellence center of the regional health service, that sets up cannabis preparations for the patients of the entire local health Toscana Centro.

scientific cooperation with national and international bodies

The project is carried out in scientific collaboration with two External Research Organization:

- The Higher Institute of Health, also **ISS**, is a public, technical-scientific body of the National Health Service, carrying out research, experimentation, control, consulting, documentation and training in the field of public health. The Institute is placed under the supervision of Italian Ministry of Health and its Phytovigilance system collects all the Italian reports of suspected adverse reactions to natural products.

- **MD Anderson Cancer Center di Houston** (University of Texas, USA) is one of the original three comprehensive cancer centers in the United States. It is both a degree-granting academic institution, and a cancer treatment and research center. MD Anderson is focused on research on causes, treatments, and prevention of cancer. Prof Cohen Cohen leads a team conducting NIH-funded research and delivering clinical care of integrative medicine practices such as meditation, yoga, tai chi, massage, diet, exercise, acupuncture and other strategies such as stress management, music therapy, emotional writing and more aimed at reducing the negative aspects of cancer treatment and improving quality of life and clinical outcomes.

F) Relevance of the project assessed in terms of:

coherence with regional sectoral policies

The project is part of the Tuscany Region sectoral policies as outlined in the following measures:

- **Delibera di Giunta regionale toscana n. 1224/2016** which defines the priority areas of complementary and integrative medicine intervention including oncology and gender medicine, and establishes that the Tuscany Local Health Systems (USL) and the University Hospitals (AOUs) envisage the use of complementary medicines in the Diagnostic Therapeutic Paths of the cancer patient .

- **Delibera di Giunta regionale toscana n. 418/2015** which outlines the integration of complementary and integrative medicine in the Tuscany Oncology Network (ISPRO) according to the results of the European Commission's Joint Action research "European Partnership for Action Against Cancer" (EPAAC) to which the Tuscany Region has participated as an associated partner. The resolution also establishes that cancer patients must have the opportunity to benefit from these safe, effective and with little side effects treatments in addition to official medicine. It also establishes that the clinical research must be increased to evaluate efficacy and safety of proposed treatments and the interactions with drug therapy.

- **Piano Sanitario e Sociale Integrato Regionale 2012-2015** which includes complementary and integrative therapies in the fight against cancer, in particular for the treatment of adverse effects, according to the indications of the international literature. Complementary medicines (phytotherapy, acupuncture, homeopathy and manual medicine) become an integral and innovative part of the Tuscan Regional Health Service; since 2005 they are part of the regional LEA (Resolution G.R. No. 655/2005).

- **Delibera di Giunta regionale toscana n. 159/2014** adhesion of the Tuscany Region to the CanCon Project conducting to the publication of the European guide on quality improvement in comprehensive cancer control (2017). It shows how the use of complementary medicine should be appropriately studied in the management of the side effects of the therapy.

The attention to the issue of pain in healthcare has also been the subject of a national law in 2010, the law 38 "Access to Pain Therapy and Palliative Care" which establishes the right of citizens do not to suffer unnecessarily. The Complementary Medicines have always found a wide use in the treatment of pain. In particular, the Phytotherapy can effectively integrate the current therapies, also ensuring the safety of the user. The appeal of the population to these methods of treatment is constantly growing. For these reasons, this project represents an innovative resource that the Tuscany health system can use meeting the citizen needs.

consistency with the purpose of the Call

The project is consistent with the purpose of the Call since it is oriented to the qualitative growth of the regional assistance levels, evaluating the effectiveness of a phytotherapy with galenic preparations based on Cannabis to reduce the resistant pain to conventional therapy. Thus, it will improve the adherence to aromatase inhibitor therapy, often abandoned due to the persistence of pain induced by the drugs themselves.

The project also includes a multidisciplinary partnership (AOU Careggi, ISPRO, Azienda USL Toscana Centro and University of Florence) and a brilliant scientific collaboration (ISS and MD

Anderson Cancer Center).

potential transferability and spillover to the Regional Healthcare System (SSR)

Phytotherapy in the oncological field (integrative oncology) in the Tuscan Health System is already present as foreseen by the regional guidelines (DGR n. 418/2015 and DGR n. 1224/2016). Thus, the results of the present project will be easily transferred in the SSR and made usable to citizens according to the legislation that foresees the use of Cannabis in the treatment of pain charged to the NHS.

patient and association engagement

This project has been object of a expression of interest (attached) by the no profit "Association Luca Coscioni" (Registro APS n. 0124) having among its priorities the affirmation of civil liberties and human rights, access to medical cannabinoids and the global monitoring of laws and policies on science and self-determination.

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ALLEGATO B1

BANDO SALUTE 2018
TosCANNABIS

DIAGRAMMA DI GANTT 1 – 18 MONTHS

OO / Activity Definition		Project Time (Months)																	
OO / Activity	OO Name / Activity	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
OO1	Study population																		
Activity 1.1	Patient recruitment	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
Activity 1.2	Information retrieval	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
OO2	Pain management																		
Activity 2.1	Pain intensity assessment	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
Activity 2.2	Pain treatment	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
OO3	Galenic formulations of Cannabis																		
Activity 3.1	Olive oil (FU) extraction of female Cannabis inflorescence	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Activity 3.2	Cannabinoid determination in oil extract by HPLC/DAD	D			D			D			D			D			D		
OO4	Pharmacokinetic evaluations																		
Activity 4.1	Blood sample collection	x	x	x	x	x	x												
Activity 4.2	Cannabinoid determination in blood samples by LC-MS/MS					x	x	x	x	x	D	x	x	x	x	x	D		
OO5	Follow up																		
Activity 5.1	Clinical visit at T0	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
Activity 5.2	Clinical visit at T1 – T3 – T6 - T12	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
OO6	Pharmacovilance																		
Activity 6.1	Safety assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Activity 6.2	AEs evaluation	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Activity 6.3	AEs reporting	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
OO7	Phytovigilance																		
Activity 7.1	Cannabis Adverse Reactions (ARs) collection	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Activity 7.2	Cannabis ARs evaluation	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
OO8	Data analysis																		
Activity 8.1	Data entry													x	x	x	x	x	D
Activity 8.2	Statistical data analysis																		
OO9	Study results																		
Activity 9.1	Discussion of the results																		
Activity 9.2	Study final report and dissemination																		

Steps of deliverables are highlighted in the GANTT diagram with D letter

DIAGRAMMA DI GANTT 19 – 36 MONTHS

ALLEGATO B1

BANDO SALUTE 2018
TosCANNABIS

OO / Activity Definition		Project Time (Months)																	
OO / Activity	OO Name / Activity	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
OO1	Study population																		
Activity 1.1	Patient recruitment																		
Activity 1.2	Information retrieval	x	x	x	x	x	D	x	x	x	x	x	D						
OO2	Pain management																		
Activity 2.1	Pain intensity assessment	x	x	x	x	x	D	x	x	x	x	x	D						
Activity 2.2	Pain treatment	x	x	x	x	x	D	x	x	x	x	x	D						
OO3	Galenic formulations of Cannabis																		
Activity 3.1	Olive oil (FU) extraction of female Cannabis inflorescence	x	x	x	x	x	x	x	x	x	x	x	x						
Activity 3.2	Cannabinoid determination in oil extract by HPLC/DAD	D			D			D			D								
OO4	Pharmacokinetic evaluations																		
Activity 4.1	Blood sample collection																		
Activity 4.2	Cannabinoid determination in blood samples by LC-MS/MS																		
OO5	Follow up																		
Activity 5.1	Clinical visit at T0	x	x	x	x	x	D	x	x	x	x	x	D						
Activity 5.2	Clinical visits from T1 to T6	x	x	x	x	x	D	x	x	x	x	x	D						
OO6	Pharmacovilance																		
Activity 6.1	Safety assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Activity 6.2	AEs evaluation	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Activity 6.3	AEs reporting	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
OO7	Phytovigilance																		
Activity 7.1	Cannabis Adverse Reactions (ARs) collection	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Activity 7.2	Cannabis ARs evaluation	x	x	x	x	x	D	x	x	x	x	x	D	x	x	x	x	x	D
OO8	Data analysis																		
Activity 8.1	Data entry	x	x	x	x	x	D	x	x	x	x	x	D						
Activity 8.2	Statistical data analysis							x	x	x	x	x	D	x	x	x			
OO9	Study results																		
Activity 9.1	Discussion of the results							x	x	x	x	x	x	x	x	D	x	x	x
Activity 9.2	Study final report and dissemination																x	x	D

Specify, in relation to the scheduled activities, the results obtained periodically (deliverables), based on what is indicated in section 3 of the project data sheet (annex B) Steps of deliverables are highlighted in the GANTT diagram with D letter

ALLEGATO B2 BANDO RICERCA SALUTE 2018

80,00%

ACRONIMO PROGETTO TosCANNABIS

TABELLA 1: COSTO TOTALE DEL PROGETTO:

COMPOSIZIONE DEI COSTI DEL PROGETTO DI RICERCA	COSTO TOTALE PROGETTO	% MAX	CONTRIBUTO TOTALE RICHIESTO	% RISPETTO AL COSTO COMPLESSIVO DI PROGETTO	
PERSONALE STRUTTURATO	€ 70.000,00	20%	**NON FINANZIABILE**	**20,00%**	**OK**
PERSONALE A TERMINE PER ATTIVITA' DI RICERCA E SVILUPPO RECLUTATO SPECIFICATAMENTE PER IL PROGETTO	€ 169.000,00		€ 169.000,00	**48,29%**	
STRUMENTAZIONI E ATTREZZATURE	€ 0,00		€ 0,00	**0,00%**	
MATERIALE DI CONSUMO	€ 45.000,00		€ 45.000,00	**12,86%**	
COSTI DEI SUBCONTRATTI, COSTI DEI BREVETII ACQUISITI O OTTENUTI IN LICENZA DA FONTI ESTERNE A PREZZI DI MERCATO, COSTI RELATIVI AL COMITATO ETICO, COSTI DEI SERVIZI DI CONSULENZA O SERVIZI EQUIVALENTI	€ 6.000,00	10%	€ 6.000,00	**1,71%**	**OK**
TRIAL CLINICI	€ 25.000,00		€ 25.000,00	**7,14%**	
DIFFUSIONE E TRASFERIMENTO DEI RISULTATI	€ 7.250,00	5%	€ 6.250,00	**2,07%**	**OK**
TRASFERTE E MISSIONI DEGLI OR PARTECIPANTI	€ 4.000,00	5%	€ 4.000,00	**1,14%**	**OK**
TRASFERTE E MISSIONI DEI BENEFICIARI	€ 10.000,00	3%	€ 10.000,00	**2,86%**	**OK**
OVERHEAD	€ 13.750,00	5%	€ 13.750,00	**3,93%**	**OK**
TOTALE	**€ 350.000,00**		**€ 279.000,00**		**OK**

TABELLA2: COSTI SOSTENUTI DA CAPOFILA (PARTNER 1) indicare ragione sociale

COMPOSIZIONE DEI COSTI DEL PROGETTO DI RICERCA	COSTO PROGETTO	% MAX	CONTRIBUTO TOTALE RICHIESTO	% RISPETTO AL COSTO COMPLESSIVO DI PROGETTO	
PERSONALE STRUTTURATO	€ 36.000,00	20%	**NON FINANZIABILE**	**20,00%**	**OK**
PERSONALE A TERMINE PER ATTIVITA' DI RICERCA E SVILUPPO RECLUTATO SPECIFICATAMENTE PER IL PROGETTO	€ 114.000,00		€ 114.000,00		
STRUMENTAZIONI E ATTREZZATURE					
MATERIALE DI CONSUMO					
COSTI DEI SUBCONTRATTI, COSTI DEI BREVETII ACQUISITI O OTTENUTI IN LICENZA DA FONTI ESTERNE A PREZZI DI MERCATO, COSTI RELATIVI AL COMITATO ETICO, COSTI DEI SERVIZI DI CONSULENZA O SERVIZI EQUIVALENTI	€ 6.000,00		€ 6.000,00		
TRIAL CLINICI	€ 5.000,00		€ 5.000,00		
DIFFUSIONE E TRASFERIMENTO DEI RISULTATI	€ 3.000,00		€ 3.000,00		
TRASFERTE E MISSIONI DEGLI OR PARTECIPANTI	€ 3.000,00		€ 3.000,00		
TRASFERTE E MISSIONI DEI BENEFICIARI	€ 4.000,00		€ 3.000,00		
OVERHEAD	€ 9.000,00	5%	€ 9.000,00	**5,00%**	**OK**
TOTALE	**€ 180.000,00**		€ 143.000,00		**OK**

TABELLA2: COSTI SOSTENUTI DA PARTNER 2 ISPRO

COMPOSIZIONE DEI COSTI DEL PROGETTO DI RICERCA	COSTO PROGETTO	% MAX	CONTRIBUTO TOTALE RICHIESTO	% RISPETTO AL COSTO COMPLESSIVO DI PROGETTO	
PERSONALE STRUTTURATO	€ 7.000,00	20%	**NON FINANZIABILE**	**20,00%**	**OK**
PERSONALE A TERMINE PER ATTIVITA' DI RICERCA E SVILUPPO RECLUTATO SPECIFICATAMENTE PER IL PROGETTO					
STRUMENTAZIONI E ATTREZZATURE					
MATERIALE DI CONSUMO					
COSTI DEI SUBCONTRATTI, COSTI DEI BREVETII ACQUISITI O OTTENUTI IN LICENZA DA FONTI ESTERNE A PREZZI DI MERCATO, COSTI RELATIVI AL COMITATO ETICO, COSTI DEI SERVIZI DI CONSULENZA O SERVIZI EQUIVALENTI					
TRIAL CLINICI	€ 20.000,00		€ 20.000,00		
DIFFUSIONE E TRASFERIMENTO DEI RISULTATI	€ 2.250,00		€ 1.250,00		
TRASFERTE E MISSIONI DEGLI OR PARTECIPANTI					
TRASFERTE E MISSIONI DEI BENEFICIARI	€ 4.000,00		€ 5.000,00		
OVERHEAD	€ 1.750,00	5%	€ 1.750,00	**5,00%**	**OK**
TOTALE	**€ 35.000,00**		€ 28.000,00		**OK**

TABELLA2: COSTI SOSTENUTI DA PARTNER 3 UNIFI

COMPOSIZIONE DEI COSTI DEL PROGETTO DI RICERCA	COSTO PROGETTO	% MAX	CONTRIBUTO TOTALE RICHIESTO	% RISPETTO AL COSTO COMPLESSIVO DI PROGETTO	
PERSONALE STRUTTURATO	€ 12.000,00	20%	**NON FINANZIABILE**	**20,00%**	**OK**
PERSONALE A TERMINE PER ATTIVITA' DI RICERCA E SVILUPPO RECLUTATO SPECIFICATAMENTE PER IL PROGETTO	€ 40.000,00		€ 40.000,00		
STRUMENTAZIONI E ATTREZZATURE					
MATERIALE DI CONSUMO					
COSTI DEI SUBCONTRATTI, COSTI DEI BREVETII ACQUISITI O OTTENUTI IN LICENZA DA FONTI ESTERNE A PREZZI DI MERCATO, COSTI RELATIVI AL COMITATO ETICO, COSTI DEI SERVIZI DI CONSULENZA O SERVIZI EQUIVALENTI					
TRIAL CLINICI					
DIFFUSIONE E TRASFERIMENTO DEI RISULTATI	€ 2.000,00		€ 2.000,00		
TRASFERTE E MISSIONI DEGLI OR PARTECIPANTI	€ 1.000,00		€ 1.000,00		
TRASFERTE E MISSIONI DEI BENEFICIARI	€ 2.000,00		€ 2.000,00		
OVERHEAD	€ 3.000,00	5%	€ 3.000,00	**5,00%**	**OK**
TOTALE	**€ 60.000,00**		€ 48.000,00		**OK**

TABELLA2: COSTI SOSTENUTI DA PARTNER 4 Azienda USL Toscana Centro

COMPOSIZIONE DEI COSTI DEL PROGETTO DI RICERCA	COSTO PROGETTO	% MAX	CONTRIBUTO TOTALE RICHIESTO	% RISPETTO AL COSTO COMPLESSIVO DI PROGETTO	
PERSONALE STRUTTURATO	€ 15.000,00	20%	**NON FINANZIABILE**	**20,00%**	**OK**
PERSONALE A TERMINE PER ATTIVITA' DI RICERCA E SVILUPPO RECLUTATO SPECIFICATAMENTE PER IL PROGETTO	€ 15.000,00		€ 15.000,00		
STRUMENTAZIONI E ATTREZZATURE					
MATERIALE DI CONSUMO	€ 45.000,00		€ 45.000,00		
COSTI DEI SUBCONTRATTI, COSTI DEI BREVETII ACQUISITI O OTTENUTI IN LICENZA DA FONTI ESTERNE A PREZZI DI MERCATO, COSTI RELATIVI AL COMITATO ETICO, COSTI DEI SERVIZI DI CONSULENZA O SERVIZI EQUIVALENTI					
TRIAL CLINICI					
DIFFUSIONE E TRASFERIMENTO DEI RISULTATI					
TRASFERTE E MISSIONI DEGLI OR PARTECIPANTI					
TRASFERTE E MISSIONI DEI BENEFICIARI					
OVERHEAD		5%		**0,00%**	**OK**
TOTALE	**€ 75.000,00**		€ 60.000,00		**OK**

Partner	Denominazione partner	Costi sostenuti da ciascun partner	% di partecipazione ai costi del progetto di ciascun partner		Contributo richiesto
CAPOFILA (PARTNER 1)	indicare ragione sociale	€ 180.000,00	51,43%	**OK**	€ 143.000,00
PARTNER 2	ISPRO	€ 35.000,00	10,00%	**OK**	€ 28.000,00
PARTNER 3	UNIFI	€ 60.000,00	17,14%	**OK**	€ 48.000,00
PARTNER 4	Azienda USL Toscana Centro	€ 75.000,00	21,43%	**OK**	€ 60.000,00
PARTNER 5	indicare ragione sociale	€ 0,00	0,00%	**PERCENTUALE DI PARTECIPAZIONE COSTI NON RISPETTATA**	€ 0,00
PARTNER 6	indicare ragione sociale	€ 0,00	0,00%	**PERCENTUALE DI PARTECIPAZIONE COSTI NON RISPETTATA**	€ 0,00
PARTNER 7	indicare ragione sociale	€ 0,00	0,00%	**PERCENTUALE DI PARTECIPAZIONE COSTI NON RISPETTATA**	€ 0,00
PARTNER 8	indicare ragione sociale	€ 0,00	0,00%	**PERCENTUALE DI PARTECIPAZIONE COSTI NON RISPETTATA**	€ 0,00
PARTNER 9	indicare ragione sociale	€ 0,00	0,00%	**PERCENTUALE DI PARTECIPAZIONE COSTI NON RISPETTATA**	€ 0,00
PARTNER 10	indicare ragione sociale	€ 0,00	0,00%	**PERCENTUALE DI PARTECIPAZIONE COSTI NON RISPETTATA**	€ 0,00
TOTALE		**€ 350.000,00**			**€ 279.000,00**