# DETERMINAZIONE DEL DIRETTORE GENERALE

**n. 351 DG del 13 AGO 2019**

## OGGETTO

## APPROVAZIONE DELL'AMENDMENT N. 1 ALL'ACCORDO CON "EUROPEAN PALLIATIVE CARE RESEARCH CENTRE", NORVEGIA, PER L'ESECUZIONE DI ATTIVITA' CORRELATE AL PROGETTO DI RICERCA "EVIDENCE-BASED KNOWLEDGE IMPROVEMENT IN PALLIATIVE CARE".

Attestazione di legittimità e regolarità dell'istruttoria

Il dirigente della struttura semplice
Trasferimento Tecnologico (TTO)
(dott. Antonio Cannarozzo)

In base alle attestazioni rese dal dirigente competente all'adozione del provvedimento e alle verifiche contabili svolte:

☑ si provvede alle registrazioni contabili.
☐ il provvedimento non comporta registrazioni contabili, né impegni finanziari futuri.

Il dirigente della struttura complessa
Risorse Economiche e Finanziarie e Libera Professione
(dott. Giacomo Boscagli)

| CON I PARERI FAVOREVOLI DEL | | |
|---|---|---|
| **Direttore Scientifico** | **Direttore Amministrativo** | **Direttore Sanitario** |
| dott. Giovanni Apolone | dott. Andrea Frignani | dott. Oliviero Rinaldi |

L'atto si compone di 16 pagine di cui 12 pagine di allegati parte integrante
atti n. *1.6.05.02-297/2010*/p.l.

FONDAZIONE IRCCS
Istituto Nazionale Tumori
VERCOL

s.c. Affari Generali e Legali
IL DIRETTORE

## IL DIRETTORE GENERALE

su proposta del Responsabile del procedimento della s.s. Trasferimento Tecnologico (TTO) che, a seguito di istruttoria, attesta:

**premesso**

- che tra la Fondazione e il centro europeo "European Palliative Care Research Centre" (PRC), Trondheim, Norvegia, ora presso il Department of Oncology, Oslo University Hospital, Ullevål, PO 4956, Nydalen, 0424 Oslo, Norvegia, si è sviluppata negli anni una collaborazione, di cui alle deliberazioni 16 novembre 2010 n. 85F e 20 dicembre 2013 n. 136F, finalizzata all'attivazione di un progetto di cooperazione scientifica, accademica e culturale nel campo delle cure palliative, sotto la responsabilità scientifica del dott. Augusto Tommaso Caraceni, Dirigente della s.c. Cure Palliative, Terapia del Dolore e Riabilitazione della Fondazione;
- che, nell'ambito della collaborazione sopracitata, con determinazione 14 dicembre 2015 n. 353DG, le Parti hanno sottoscritto un accordo per la conduzione del Programma di ricerca triennale denominato "*Evidence-based knowledge improvement in Palliative Care*", finalizzato all'implementazione della conoscenza nel campo delle cure palliative, basata sull'evidenza della pratica clinica, per migliorare le condizioni dei pazienti oncologici e delle loro famiglie";

**atteso** che, alla luce dei proficui risultati ottenuti nell'ambito del sopracitato Programma di ricerca denominato "*Evidence-based knowledge improvement in Palliative Care*":

- con nota 15 ottobre 2018, il prof. Stein Kaasa, in qualità di Direttore del "European Palliative Care Research Centre", ha comunicato al dott. Augusto Tommaso Caraceni, in qualità di Responsabile Scientifico per la Fondazione, l'intenzione di proseguire le attività oltre la scadenza del 31 dicembre 2018, per ulteriori due anni, riconoscendo alla Fondazione un contributo complessivo pari ad € 50.000,00;
- con e-mail 22 ottobre 2018, il dott. Augusto Tommaso Caraceni ha trasmesso la sopracitata nota del prof. Stein Kaasa, esprimendo parere favorevole alla proroga dell'accordo

**vista** la nota 31 ottobre 2018 con la quale il Responsabile Scientifico ha trasmesso la seguente documentazione depositata in atti:

- il programma delle attività da condurre nei due anni di proroga dell'accordo;
- il piano di spesa, debitamente approvato dalle strutture aziendali competenti, dal quale risulta un costo complessivo di progetto pari ad € 140.000,00 suddiviso come segue:
  1. finanziamento pari ad € 25.000 all'anno per due anni, per un totale di € 50.000,00;
  2. un cofinanziamento a carico della Fondazione pari ad € 90.000,00 da imputare come segue:
     - ✓ € 38.000,00 al codice identificativo interno n. U/05/191,
     - ✓ € 52.000,00 al codice identificativo interno n. D/17/1/CB sottobudget 2018003737;

s.c. Affari Generali e Legali
IL DIRETTORE



20133 Milano - via Venezian, 1 - tel. 02.2390.1 - codice fiscale 80018230153 - partita i.v.a. 04376350155

- il parere favorevole del Direttore di Dipartimento di Area critica e di supporto e del Direttore Scientifico;

**visto** il testo di Amendment n. 1, pervenuto debitamente sottoscritto da European Palliative Care Research Centre (PRC), presso il Department of Oncology, Oslo University Hospital, Ullevål, PO 4956, Nydalen, 0424 Oslo, Norvegia, in data 5 luglio 2019, e dal Responsabile Scientifico della Fondazione in data 31 luglio 2019, nella versione concordata con la s.s. Trasferimento Tecnologico (TTO), allegata al presente provvedimento di cui forma parte integrante e sostanziale;

**dato atto** che, come risulta dal piano di spesa, il costo complessivo di progetto pari ad € 140.000,00 è suddiviso per voci analitiche di spesa, come segue:
- € 138.082,00 per personale non dipendente per l'intera durata biennale del progetto;
- € 1.918,00 per viaggi e trasferte;

**preso atto**
- che l'Amendment n. 1 prevede il rinnovo biennale del Programma di cui trattasi, dal 1° gennaio 2019 fino al 31 dicembre 2020;
- delle modalità di erogazione del contributo indicate all'art. 4a) dell'Amendment

**considerato** altresì che nulla osta alla pubblicazione del presente provvedimento in versione integrale all'Albo Pretorio della Fondazione, per 15 giorni consecutivi, ai sensi dell'art. 32 della L. n. 69/2009 e della L.R. n. 33/2009 nel testo vigente;

**dato atto** dell'attestazione di regolarità dell'istruttoria sia sotto il profilo tecnico che di legittimità, nonché delle disposizioni finanziarie e contabili;

**richiamata** la determinazione del Direttore Generale n. 311DG del 29 settembre 2017, avente ad oggetto "Disposizioni a carattere gestionale del Direttore Generale";

**visti** i pareri favorevoli dei Direttori Scientifico, Amministrativo e Sanitario della Fondazione resi per quanto di competenza,

DETERMINA

1- di approvare l'Amendment n. 1, di durata biennale fino al 31 dicembre 2020, allegato al presente provvedimento di cui forma parte integrante e sostanziale, da stipularsi con European Palliative Care Research Centre (PRC), presso il Department of Oncology, Oslo University Hospital, Ullevål, PO 4956, Nydalen, 0424 Oslo, Norvegia all'accordo per la conduzione del Programma di ricerca triennale denominato "*Evidence-based knowledge improvement in Palliative Care*", sotto la responsabilità scientifica del dott. Augusto Tommaso Caraceni, Dirigente della s.c. Cure Palliative, Terapia del Dolore e Riabilitazione della Fondazione, approvato con determinazione n. 353DG/2015;
2- che il finanziamento riconosciuto alla Fondazione, pari ad € 25.000 all'anno per due anni, per un totale di € 50.000,00, oltre IVA se e in quanto dovuta, verrà introitato in conformità al piano di spesa e al dispositivo n. 2 della determinazione n. 353DG/2015, sul conto di bilancio degli esercizi di competenza n. 70104010 "Contributo in conto esercizio da enti privati", a

s.c. Affari Generali e Legali
DIRETTORE


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disposizione della s.c. Cure Palliative, Terapia del Dolore e Riabilitazione della Fondazione, codice identificativo interno n. H/15/004;

3. che il cofinanziamento a carico della Fondazione pari ad € 90.000,00 verrà imputato, in conformità al piano di spesa depositato in atti, come segue:
   - ✓ € 38.000,00 al codice identificativo interno n. U/05/191,
   - ✓ € 52.000,00 al codice identificativo interno n. D/17/1/CB sottobudget 2018003737;
4. di individuare il Responsabile Scientifico quale Direttore dell'Esecuzione del Contratto, con particolare riferimento alla corretta tempistica della fatturazione, al relativo monitoraggio, nonché Responsabile del trattamento dei dati oggetto delle attività di ricerca in argomento;
5. di disporre la pubblicazione del presente provvedimento all'Albo Pretorio della Fondazione, per 15 giorni consecutivi, ai sensi dell'art. 32 della L. n. 69/2009 e della L.R. n. 33/2009 nel testo vigente.

IL DIRETTORE GENERALE
Dott. Stefano Manfredi

s.c. Affari Generali e Legali



20133 Milano - via Venezian, 1 - tel. 02.2390.1 - codice fiscale 80018230153 - partita i.v.a. 04376350155

# AMENDMENT N. 1

This Amendment n. 1 is entered into on the date of the last signature ("Effective Date") by and between

**European Palliative Care Research Centre** at the Department of Oncology, Oslo University Hospital, Oslo, Norway, whose address is Oslo University Hospital, Ullevål, PO 4956, Nydalen, 0424 Oslo, Norway, hereby duly represented by Director Prof. Stein Kaasa (hereinafter called **"PRC"**)

**and**

**Fondazione IRCCS Istituto Nazionale dei Tumori**, whose address is at Via Giacomo Venezian 1, 20133 Milano, Italy, hereby duly represented by its General Manager, Dr. Stefano Manfredi, (hereinafter called "**INT**")
hereinafter collectively referred to as the Parties,

hereinafter jointly referred to as the **"Parties"**

WHEREAS

- on November 16th, 2010 the Parties entered into a three-year Framework Agreement, renewed on December 20th, 2013 and on March 27th, 2017, whereby, in recognition of their common interests in improving palliative care for cancer patients, they wish to pursue in implementing "Collaborative Research Programs" to be defined in specific agreements;
- on December 14th, 2015 within the Framework Agreement, the Parties have entered into a three-year Agreement for the execution of the project "*Evidence-based knowledge improvement in Palliative Care*", due to expire on December 31st, 2018;
- on October 15th, 2018 PRC has expressed its interest in pursuing the activities of the Project;
- on November 29th, 2018 the Scientific Director and the Director of Dipartimento di Area critica e di supporto (Department of Anaesthesia, Intensive Care, Pain Therapy and Palliative Care) of INT have approved the research program described in the Annex 2 "Evidence-based knowledge improvement in Palliative Care", Vers. 2018-10-31 (the "Project"), attached herein;
- the Parties agree to extend the Agreement;

**the Parties agree as follows**

1. the preamble constitutes an integral and essential part of this Amendment.
2. This Amendment will run as from the Effective Date until December 31st 2020, as the date of Project activities' conclusion. This Amendment may be modified or extended by mutual written agreement between the Parties.
3. the Project starts on 1st of January 2019 for a duration of two years.
4. for the execution of the Project' activities, described in Annex 2:

a) subsequent to the Effective Date, PRC will grant INT a contribution of € 25.000,00 (twenty-five thousand/00) per year for 2 years,
   - ✓ the sum of € 25.000,00 (twentyfive-thousand/00) for year 2019 will be wired by PRC immediately upon receipt of an appropiate debit note from INT;

- ✓ the sum of € 25.000,00 (twentyfive-thousand/00) for year 2020 will be wired by PRC at the end of the first year immediately upon receipt of an appropriate debit note from INT.
  PRC's accounting address and INT Bank details are given in Annex 1;

b) INT will also contribute with a cofinancing equal to € 90.000,00 (ninetythousand/00) as follows:
   - ✓ € 38.000,00 (thirty-eight thousand/00), INT internal reference code U05191;
   - ✓ € 52.000,00 (fifty-two thousand/00), INT internal reference code D/17/1/CB (sottobudget 2018003737).

This amendment is drawn up in two originals, one for each Party.

IN WITNESS WHEREOF, the Parties have caused this Amendment n. 1 to be executed by their duly authorized representatives.

**For PRC**:
Director
Prof. Stein Kaasa
Date: 20/6/19

Professor Stein Kaasa
Head of Department of Oncology
Director European Palliative Care Research Center
Scientific Responsible

**For INT**:
General Manager
Dr. Stefano Manfredi
Date: _____

For acknowledgement and acceptance:
31/07/2019
Dr. Augusto Tommaso Caraceni
Direttore s.c. Cure Palliative,
Terapia del Dolore e Riabilitazione

Scientific Responsible

Encl.:
Annex 1 - PRC's accounting address and INT Bank details
Annex 2 – The Project

**ANNEX 1**

**PRC Financial information**
**PRC accounting address**
Oslo University Hospital
Department of Oncology
Oslo - Norway

The invoice has to be marked with:
Project number: 31086, source: 6220
European Palliative Care Research Centre

INT financial information
Bank and address
Banca Popolare di Sondrio
Ag. 21 Politecnico
via Edoardo Bonardi 4 – 20133 Milano - Italy
Account number and SWIFT-code
IBAN code: IT15C0569601620000002001X82
SWIFT code: POSOIT22XXX
**To be mentioned in the bank transfer: INT internal reference code H/15/004**

**ANNEX 2**

# "EVIDENCE-BASED KNOWLEDGE IMPROVEMENT IN PALLIATIVE CARE" (THE "PROJECT")

Fondazione IRCCS Istituto Nazionale dei Tumori – Milano

and

European Palliative Care Research Centre, – Oslo University Hospital - Oslo

## OVERALL AIM

This project builds on the framework agreement established between the Fondazione IRCCS Istituto Nazionale dei Tumori (IRCCS-INT) and the European Palliative Care Research Centre's (PRC) NTNU - Trondheim in 2010 and renewed in 2016. The overall aim of the scientific collaboration between two institutions is to increase evidence-base knowledge for the improvement of palliative care for cancer patients and their families and to promote implementation of evidence into clinical practice through development of treatment guidelines and of integrated care pathways via an European international collaborative.

**Prioritised research areas within the collaboration:**

I. Health care improvements based on the development, implementation and evaluation of guidelines for symptom management and of integrated care pathways.
II. Basic/translational research in palliative care in cancer, including genetics and prognostication.
III. Assessment and classification of common symptoms in cancer patients also via new ICT devices; research will mainly focus on: pain, cachexia and depression.
IV. Testing efficacy and tolerability of palliative care therapies in randomised controlled trials as well as in observational studies.

Within this area of collaboration the PRC and the Struttura Complessa di Cure Palliative, Terapia del Dolore e Riabilitazione of the IRCCS-INT (PC Unit), will share common research projects and specific expertise in the areas of trial design, protocol writing, statistical analysis, funding applications, article writing and publishing in peer reviewed journals.

For the implementation of these collaborations, the OUH and the Fondazione IRCCS Istituto Nazionale dei Tumori plan to fund a position at the PC Unit for a senior researcher with a specific expertise in biostatistics and palliative care research.

## RESEARCH PROJECTS ALREADY ONGOING OR PLANNED WITHIN RESEARCH AREAS

The following is a list of research projects already ongoing or planned, which are examples of the current and future collaboration. For some of the project activities, already approved or not in need of approval by Ethical Committee, an established workplan is already in place. For projects still in the planning phase, the PRC and the PC Unit will identify how to employ the shared professional resources after approval of Institutional Ethical and Scientific committee when requested, depending upon the type of collaboration.

## HEALTH CARE IMPROVEMENTS

### *EAPC GUIDELINES ON CANCER PAIN MANAGEMENT*

**Aims and methods**

The aim of this project is to update the European Association for Palliative Care (EAPC) guidelines on the "Use of opioids for cancer pain management"(Caraceni 2012) and to integrate them with a series of new topics to broaden their scope to "Cancer pain management". Guidelines will be based on a set of systematic reviews that will summarize available evidence regarding the treatment of cancer pain. The review process and recommendation formulation will be carried out in agreement respectively with the PRISMA statement for systematic reviews preparation and with the GRADE system for guidelines development. The whole set of systematic reviews was registered on PROSPERO (registration number CRD42014009150), http://www.crd.york.ac.uk/PROSPERO.

**Project timeline** 2014-2019

***Update at Oct 2018:*** manuscript writing.

### *ORKDAL MODEL STUDY*

**Aims and methods**

The Orkdal Model is an integrated model of palliative cancer care established in Orkdal, Mid-Norway. It consists of a standardised care pathway coordinating care within and between specialist and community care, and of an educational/informative programme for healthcare providers, patients, their families and the general public. The target population is cancer patients with metastatic and/ or loco-regional disease. The objective of this prospective controlled observational pre- post cohort study is to evaluate the effect of the Orkdal model on patient's time spent at home at the end of life, family member's health related quality of life, improvement of health care providers' knowledge and skills as well as distribution of health care service use. The

control group is constituted by cancer patient living in the catchment area of Molde Hospital.

**Project timeline** 2014-2020.
**Approved by local Ethics Committee (Regional Committee for Medical Research Ethics (REK Midt), reference number 2014/212)**

***Update at Oct 2018:*** 208 patients and 100 caregivers were enrolled. Follow-up data collection will be closed by December 2019. Baseline data related to patients caregivers have been analyzed and the paper "Spiritual wellbeing and satisfaction with care in family carers of advanced cancer patients" is currently in preparation. The main paper on place of death and place of care is expected to be sent for publication by summer 2020.

***THE PALLION STUDY***
**Aims and methods**
This multicentre cluster-randomized trial involving 12 cancer departments in four Norwegian health regions, aims at testing the effect of the integration of oncology and palliative care for cancer patients with a life expectancy <12 months undergoing chemotherapy. The intervention includes: A) systematic electronic symptom mapping, B) implementation of standardized patient pathways and C) training in palliative medicine for oncologists. Main outcomes for the comparison of intervention to standard care are: patients' psychological wellbeing, consumption of chemotherapy in life last three months of life, quality of care perceived by caregivers.
**Project timeline** 2015-2021
**Approved by local Ethics Committee (Regional Committee for Medical Research Ethics (REK sør-øst), reference number 2016/1220**

***Update at Oct 2018: data collection***

## BASIC/TRANSLATIONAL AND PROGNOSTIC PALLIATIVE CARE RESEARCH

***THE MOLO STUDY***
**Aims and methods**
This project aims at confirming preliminary results from cross-sectional data on the contribution of genetic and clinical variability to opioid analgesia in a population of cancer patients treated with strong opioids and followed up longitudinally. Genetic variants modulating opioid side effects such as nausea and vomiting will also be explored. A biobank will be established combining data from a prospective randomized controlled trial on the comparison of 4 strong opioids and data from a multicentre prospective longitudinal observational study on patients treated with the same protocol but not participating in the controlled clinical trial. A total of 800 patients will be accrued. The study will be a joined collaboration between the INT, the Mario Negri Institute in Milan, and the PRC in Oslo, Norway.

**Project timeline** 2014-2020

**Approved by local Ethics Committee (Comitato Etico della Fondazione IRCCS Istituto Nazionale Tumori - INT 153/13 and INT 36/10)**

***Update at Oct 2018:*** 582 patients have been enrolled and data collection is still ongoing. Baseline data on the prevalence of neuropathic pain diagnosed by the physician and through DN4 were analysed on 312 pts and the abstract " *Neuropathic Pain in Cancer Patients: Concordance between DN4 questionnaire and clinical evaluation.*" was sent to SICP national congress and PRC international seminar.

The following paper was submitted for publication:
*Colombo F. et al Identification of genetic polymorphisms modulating nausea and vomiting in two series of opioid-treated cancer patients*

***THE PALLIATIVE RADIOTHERAPY AND INFLAMMATION –PRAIS- STUDY***
**Aims and methods**
The primary aim of this multicenter, international longitudinal observational study is to identify potential predictors for pain relief from radiation therapy; the study will also explore predictors for development of cachexia during follow up. The study will include 1000 adult patients starting on palliative radiotherapy for bone cancer pain. Demographic data, clinical variables, genetic biomarkers and inflammatory biomarkers, assessed before start of RT will be tested as potential predictors through regression models following training and testing cross-validation methods.

**Project timeline** 2014-2019
**Approved by local Ethics Committee (Regional Committee for Medical Research Ethics (REK Midt), reference number 2013/1126 and Comitato Etico della Fondazione IRCCS Istituto Nazionale Tumori - INT 27/15)**

***Update at Oct 2018:*** Patient enrolment is now closed. 584 patients were enrolled and follow-up data collection will be closed by December 2018.

The following paper was published:
*Habberstad R, Frøseth TCS, Aass N, Abramova T, Baas T, Mørkeset ST, Caraceni A, Laird B, Boland JW, Rossi R, Garcia-Alonso E, Stensheim H, Loge JH, Hjermstad MJ, Bjerkeset E, Bye A, Lund JÅ, Solheim TS, Vagnildhaug OM, Brunelli C, Damås JK, Mollnes TE, Kaasa S, Klepstad P. The Palliative Radiotherapy and Inflammation Study (PRAIS) - protocol for a longitudinal observational multicenter study on patients with cancer induced bone pain. BMC Palliat Care. 2018 Sep 28;17(1):110. doi: 10.1186/s12904-018-0362-9. PubMed PMID: 30266081; PubMed Central PMCID: PMC6162927.*

## SYMPTOM ASSESSMENT AND CLASSIFICATION

***EPISODIC PAIN ASSESSMENT AND CLASSIFICATION. A DELPHI STUDY***
**Aims and methods**
An international Delphi survey was undertaken with the overall aim of assessing and increasing agreement on definition, diagnosys and classification of transient cancer pain exacerbations among international pain experts, A two-round modified Delphi survey was performed from February to May 2015. Participants were identified among authors and co-authors on the subject over the past ten years; issues considered in the survey were formulated into twenty statements and further refined by a task force of pain

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experts on behalf of the European Association for Palliative Care Research Network (EAPC RN). Participants were asked to rate their degree of agreement with the statements on 0-10 NRSs and consensus was defined as a median NRS (0-10) score of seven or more and an IQR of three or less.

**Project timeline** 2014-2016
**Approoval by local Ethics Committee not required.**

***Update at Oct 2018:*** study completed
*Lohre ET, Klepstad P, Bennett MI, Brunelli C, Caraceni A, Fainsinger RL, Knudsen AK, Mercadante S, Sjogren P, Kaasa S, European Assoc Palliative Care Res. From "Breakthrough" to "Episodic" Cancer Pain? A European Association for Palliative Care Research Network Expert Delphi Survey Toward a Common Terminology and Classification of Transient Cancer Pain Exacerbations. J Pain Symptom Manage 2016;51:1013-1019.*

***EIR, AN ELECTRONIC PATIENT REPORTED OUTCOMES ASSESSMENT TOOLD AND COMPUTER BASED DECISION SUPPORT SYSTEM. AN INTERNATIONAL FEASIBILITY STUDY***

**Aims and methods**

The EIR system is a combination of electronic patient reported symptom assessment and computer based clinical decision support tools. It consists of several modules, for outpatients, patients at home, and health care providers. The information collected through the patient modules on multiple devices (mobile phone, tablet or computer) is wirelessly transferred and immediately available for the health care provider (HCP) in a separate HCP module.
This international prospective observational pilot study is aimed assessing functionality, acceptability and comprehensibility of EIR. The study is planned enroll 150 patients in the following countries: Norway, Italy, Denmark, Great Britain, and Switzerland. Both qualitative and quantitative research methods will be applied in the assessment of the study endpoints.

**Project timeline** 2014-2017
**Approved by local Ethics Committee (Regional Committee for Medical Research Ethics (REK Midt), reference number 2015/185)**

***Update at Oct 2018:*** study completed
*Krogstad, H., Brunelli, C., Sand, K., Andersen, E., Garresori, H., Halvorsen, T., ... & Løhre, E. T. (2017). Development of EirV3: A Computer-Based Tool for Patient-Reported Outcome Measures in Cancer.JCO Clinical Cancer Informatics,1, 1-14.*

***PATIENT VOICES: A PROJECT FOR THE INTEGRATION OF SYSTEMATIC ASSESSMENT OF PATIENT REPORTED OUTCOMES WITHIN AN E-HEALTH PROGRAMM IN AN ITALIAN COMPREHENSIVE CANCER CENTER***

**Aims and methods**

This project is aimed at achieving a stepwise inclusion and integration of patient reported outcomes (PROMs) within the electronic medical record (EMR). The project will be developed on three phases: pilot and feasibility testing (phase I), implementation (phase II) and impact measurement (phase III). Phase I presently being carried out and it has the following aims: assessing the use and attitudes toward PROMs in oncological IRCCSs in Italy; reviewing pre-existing ePROMS assessment systems and exploring

technical feasibility of ePROMs integration into EMR; developing and pilot testing a flexible system for electronic collection of PROMs; assessing feasibility of ePROM assessment of physical symptoms, psychological distress and patient satisfaction; identifying barriers to and developing strategies for the final implementation and integration of routine ePROMs into the EMR. A mixed method approach (qualitative and quantitative studies) will be followed to address aims listed above.

**Project timeline** 2018-2020
**Approved by local Ethics Committee (Comitato Etico della Fondazione IRCCS Istituto Nazionale Tumori - INT 167/18)**

***Update at Oct 2018:*** Focus groups with patients and health care provides on knowledge, needs and attitudes about systematic PROM assessments will be carried within January 2019. Patient enrolment for the quantitative feasibility studies will start mid 2019.

## EFFICACY AND TOLERABILITY OF PALLIATIVE CARE THERAPIES

### *SUBLINGUAL FENTANYL VERSUS SUBCUTANEOUS MORPHINE FOR THE MANAGEMENT OF SEVERE CANCER PAIN EPISODES*

**Aims and methods**

The aim of this double-blind, randomized, parallel group, two-arms, non-inferiority trial is to show non inferiority of the sublingual fentanyl (SLF) with respect to subcutaneous morphine (SCMO) for severe cancer pain episodes in patients regularly treated with opioids. 56 patients per group will be enrolled and pain intensity in the first 30 minutes after drug administration, calculated as average value of pain "right now" scores at 10, 20 and 30 minutes, will be the main outcome measure.

**Project timeline** 2013-2016
**Approved by local Ethics Committee (Comitato Etico della Fondazione IRCCS Istituto Nazionale Tumori - INT 123/13)**

***Update at Oct 2018:*** study completed

*Zecca E, Brunelli C, Centurioni F, Manzoni A, Pigni A, Caraceni A. Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial. J Clin Oncol. 2017 Mar;35(7):759-765. doi: 10.1200/JCO.2016.69.9504.*

Paper submitted for publication: *Ricchini F. et al Effect of opioid exposure on efficacy and tolerability of sublingual fentanyl and subcutaneous morphine for severe cancer pain episodes. Secondary analysis from a double-blind double dummy, randomized trial."*

### *ANALGESIC EFFICACY DURATION OF SINGLE VS DOUBLE MATRIX TRANSDERMAL FENTANYL PATCHES. A PILOT STUDY.*

Aim of this pilot study is to test the feasibility of the enrolment-blinding procedures of a double blind, parallel-group, superiority randomized controlled trial for the comparison of the duration of the analgesic efficacy of single vs double matrix transdermal fentanyl patches. Success of feasibility of the study is defined as fulfilment of the following

criteria: recruitment of at least 5 patients a month; recruitment of at least 70% of all potentially eligible patients; complete follow-up with blind fulfilment in at least 90% of all recruited subjects. All the main endpoints of the pilot study will be reported as estimated percentages along with their 95% confidence interval. Reasons of non enrolment of potentially eligible patients, and reasons of incomplete follow-up or of blindness un-fulfilment will also be collected. The sample size of 10 patients in each arm was based both ethical and logistic reasons.

**Project timeline** 2015-2017
**Approved by local Ethics Committee (Comitato Etico della Fondazione IRCCS Istituto Nazionale Tumori - INT 34/15)**

***Update at Oct 2018***
The study was interrupted due to low accrual (3 pts enrolled in 18 months) A short report is in preparation.

***MENAC: A RANDOMISED, OPEN-LABEL TRIAL OF A MULTIMODAL INTERVENTION (EXERCISE, NUTRITION AND ANTIINFLAMMATORY MEDICATION) PLUS STANDARD CARE VERSUS STANDARD CARE ALONE TO PREVENT/ATTENUATE CACHEXIA IN ADVANCED CANCER PATIENTS UNDERGOING CHEMOTHERAPY***
**Aims and methods**
The aim of this randomised phase III, open label, intervention trial, is to test efficacy and safety of a multimodal intervention (exercise, nutrition and antiinflammatory medication) in treating cachexia in cancer patients undergoing chemotherapy. Main outcome measure is weight loss (a reduced weight loss is expected in the intervention arm). A total of 240 patients will be recruited from out-patient oncology clinics at multiple sites in Europe, Canada and Australia.

**Project timeline** 2016-2020
**Approved by local Ethics Committee: Regional Committee for Medical Research Ethics (REK midt norge), reference number 2014/1130.**

***Update at Oct 2018***
By September 2018, 93 patients have been enrolled in the trial. Data collection is expected to be closed by November 2020.

## PUBLICATIONS IN COLLABORATION 2016-2018


1. *Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, Brunelli C, Caraceni A, Cervantes A, Currow DC, Deliens L, Fallon M, Gómez-Batiste X, Grotmol KS, Hannon B, Haugen DF, Higginson IJ, Hjermstad MJ, Hui D, Jordan K, Kurita GP, Larkin PJ, Miccinesi G, Nauck F, Pribakovic R, Rodin G, Sjøgren P, Stone P, Zimmermann C, Lundeby T.* ***Integration of oncology and palliative care: a Lancet Oncology Commission.*** *Lancet Oncol. 2018 Oct 17. pii: S1470-2045(18)30415-7. doi: 10.1016/S1470-2045(18)30415-7.*

2. *Lohre ET, Klepstad P, Hjermstad MJ, Knudsen AK, Brunelli C, Kaasa S* ***Pain Intensity Factors Changing Breakthrough Pain Prevalence in Patients with Advanced Cancer: A Secondary Analysis of a Cross-Sectional Observational International Study Pain and Therapy*** *IN PRESS*

3. *Habberstad R, Frøseth TCS, Aass N, Abramova T, Baas T, Mørkeset ST, Caraceni A, Laird B, Boland JW, Rossi R, Garcia-Alonso E, Stensheim H, Loge JH, Hjermstad MJ, Bjerkeset E, Bye A, Lund JÅ, Solheim TS, Vagnildhaug OM, Brunelli C, Damås JK, Mollnes TE, Kaasa S, Klepstad P.* ***The Palliative Radiotherapy and Inflammation Study (PRAIS) - protocol for a longitudinal observational multicenter study on patients with cancer induced bone pain.*** *BMC Palliat Care. 2018 Sep 28;17(1):110. doi: 10.1186/s12904-018-0362-9. PubMed PMID: 30266081; PubMed Central PMCID: PMC6162927.*

4. *Baxter JP, Fayers PM, Bozzetti F, Kelly D, Joly F, Wanten G, Jonkers C, Cuerda C, van Gossum A, Klek S, Boudreault MF, Gilbert A, Jobin M, Staun M, Gillanders L, Forbes A, O'Callaghan M, Faedo CM, Brunelli C, Mariani L, Pironi L;* ***Home Artificial Nutrition and Chronic Intestinal Failure Special Interest Group of the European Society for Clinical Nutrition and Metabolism (ESPEN). An international study of the quality of life of adult patients treated with home parenteral nutrition.*** *Clin Nutr. 2018 Aug 6. pii: S0261-5614(18)31226-3.*

5. *Musazzi UM, Rocco P, Brunelli C, Bisaglia L, Caraceni A, Minghetti P.* ***Do laws impact opioids consumption? A breakpoint analysis based on Italian sales data.*** *J Pain Res. 2018 Aug 29;11:1665-1672. doi: 10.2147/JPR.S163438. eCollection 2018.*

6. *Habberstad R, Hjermstad MJ, Brunelli C, Kaasa S, Bennett MI, Pardon K, Klepstad P.* ***Which factors can aid clinicians to identify a risk of pain during the following month in patients with bone metastases? A longitudinal analyses.*** *Support Care Cancer. 2018 Aug 13. doi: 10.1007/s00520-018-4405-9.*

7. *Vagnildhaug OM, Balstad TR, Almberg SS, Brunelli C, Knudsen AK, Kaasa S, Thronæs M, Laird B, Solheim TS.* ***A cross-sectional study examining the prevalence of cachexia and areas of unmet need in patients with cancer.*** *Support Care Cancer. 2018 Jun;26(6):1871-1880.*

8. *Krogstad, H., Brunelli, C., Sand, K., Andersen, E., Garresori, H., Halvorsen, T., ... & Løhre, E. T. (2017).* ***Development of EirV3: A Computer-Based Tool for Patient-Reported Outcome Measures in Cancer.*** *JCO Clinical Cancer Informatics, 1, 1-14.*

9. *Raj SX, Brunelli C, Klepstad P, Kaasa S.* ***COMBAT study - Computer based assessment and treatment - A clinical trial evaluating impact of a computerized clinical decision support tool on pain in cancer patients.*** *Scand J Pain. 2017 Oct;17:99-106.*

10. *Zecca E, Brunelli C, Bracchi P, Biancofiore G, De Sangro C, Bortolussi R, Montanari L, Maltoni M, Moro C, Colonna U, Finco G, Roy MT, Ferrari V, Alabiso O, Rosti G, Kaasa S, Caraceni A.* ***Comparison of the Tolerability Profile of Controlled-Release Oral Morphine and Oxycodone for Cancer Pain Treatment. An Open-Label Randomized Controlled Trial.*** *J Pain Symptom Manage 2016.*

11. *Zecca E, Brunelli C, Centurioni F, Manzoni A, Pigni A, Caraceni A.* ***Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial.*** *J Clin Oncol. 2017 Mar;35(7):759-765. doi: 10.1200/JCO.2016.69.9504.*

12. *Hjermstad MJ, Aass N, Aielli F, Bennett M, Brunelli C, Caraceni A, Cavanna L, Fassbender K, Feio M, Haugen DF, Jakobsen G, Laird B, Løhre ET, Martinez M, Nabal M, Noguera-Tejedor A, Pardon K, Pigni A, Piva L, Porta-Sales J, Rizzi F, Rondini E, Sjøgren P, Strasser F, Turriziani A, Kaasa S;* ***European Palliative Care Cancer Symptom study (EPCCS). Characteristics of the case mix, organisation and delivery in cancer palliative care: a challenge for good-quality research.*** *BMJ Support Palliat Care. 2016 May 31.*

13. *Lohre ET, Klepstad P, Bennett MI, Brunelli C, Caraceni A, Fainsinger RL, Knudsen AK, Mercadante S, Sjogren P, Kaasa S, European Assoc Palliative Care Res.* ***From "Breakthrough" to "Episodic" Cancer Pain? A European Association for Palliative Care Research Network Expert Delphi Survey Toward a Common Terminology and Classification of Transient Cancer Pain Exacerbations.*** *J Pain Symptom Manage 2016;51:1013-1019.*

14. *Thronaes M, Raj SX, Brunelli C, Almberg SS, Vagnildhaug OM, Bruheim S, Helgheim B, Kaasa S, Knudsen AK.* ***Is it possible to detect an improvement in cancer pain management? A comparison of two Norwegian cross-sectional studies conducted 5 years apart.*** *Supportive Care in Cancer 2016;24:2565-2574.*