NETWORK ITALIANO
CURE DI SUPPORTO IN ONCOLOGIA

NICSO National Study: Project of Physician-Nurse Monitoring of Side Effects of Cancer Therapies

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PROTOCOL
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INVESTIGATOR'S AGREEMENT

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Approval by the Promoter and the Principal Investigators

The protocol has been revised and approved by

_____ ____/____/_____
Dr Carla Ida Ripamonti date (dd/mm/yyyy)
(Promoter Representative)

_____ ____/____/_____
Dr Carla Ida Ripamonti date (dd/mm/yyyy)
(Principal Investigator)

Local Principal Investigator

I have been revised and approved the trial

_____
(Name and Surname)

_____ ____/____/_____
date (dd/mm/yyyy)

(Local Principal Investigator)

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1. BACKGROUND

The development of cancer drug has been revolutionized in the last years, especially with the market authorization of targeted drugs and immunotherapy, both used alone or in combination with chemotherapy. The oncology pipeline has been enriched by 45 drugs from 2010 to 2014 for a total of 53 new indications (1). In a year, from November 2015 to October 2016, the Food and Drug Administration (FDA) approved 20 therapies for more than 12 different types of neoplasms (2). The use of supportive care therapies and growth factors has been increasing as well (1, 2). The existing anti-cancer therapies have produced a better and better clinical outcome for cancer patients, that is an increase in their 5-year overall survival for most tumours. To date, 68% of adults with cancer are alive at 5 years, compared to 50% in the 70s (1). In Italy, 5-year overall survival has been increasing when compared with the cases diagnosed in the previous three years in both men (57% in 2005-2007 vs 39% in 1990-1992) and women (63% vs 53%). This can be related to the improvement in overall survival of some of the most frequent tumours: colorectal (5-year overall survival of 64% in men and 63% in women), breast in women (87%), and prostate (91%). For some worse-prognosis tumours, the overall survival has not improved in the recent years, for example for lung tumours (14% in men and 18% in women) and pancreas tumours (7% and 9%, respectively) (3-5).

New cancer therapeutic options offer, then, better outcomes when compared with existing options and better overall survival of these patients with a low toxicity profile.

Generally speaking, cancer-related symptoms, therapy-related toxicities, and disease complications should promptly be evaluated and treated, since they negatively impact on mortality and morbidity of these patients, worsen their quality of life and increase the related costs for the National Health System. Several studies offered data on the high number of unplanned visits and/or hospital admissions due to toxicities from chemotherapy, especially about gastrointestinal issues, haematological toxicities, such as transfusion-requiring anaemia and thrombocytopenia, infections, fever and/or febrile neutropenia, but also electrolyte disorders, dyspnoea and pain (12-13).

National and international guidelines suggest the best management algorithm for the management and treatment of chemo-related toxicities, but a low adherence in everyday clinical practice can be observed, with a possible increase in the incidence and duration of adverse events, as demonstrated by several studies, especially those on the use of antiemetics (14-16, 49).

The recent development of immunotherapy has introduced a new problem related to the toxicities associated with CTLA4 and/or PD-1/PD-L1 blockade since these two pathways are involved in the regulation of the peripheral immune tolerance and are fundamental for the prevention of autoimmune problems.

To date, immune-related adverse events are graduated according to the CTCAE criteria (Common Terminology Criteria for Adverse Events) and they include a series of problems related to the immune activation, especially correlated to the activity of T lymphocytes, and they are similar to autoimmune diseases.

The most-reported toxicities are fatigue, skin problems (skin rash and pruritus), gastrointestinal problems (colitis, diarrhoea), liver issues (autoimmune hepatitis), endocrinological problems (thyroiditis, hypophysitis); less frequent the neurological issues.

However, this scenario is partially unknown and it requires the development of new tools for the evaluation of the possible consequences of these treatments, to observe the benefits in terms of overall survival, but also to evaluate the long-term effects (17-20). At the moment there are no validated predictive biomarkers that can help to identify patients at higher risk of immune-related toxicity and there is no evidence of a correlation between the toxicity development and the treatment efficacy (21).

It is fundamental that the clinician is trained about the diagnosis and the early treatment of these toxicities since an early medical intervention reduces both the severity and the duration of these problems (22).
Correct management should avail of: adequate knowledge of toxicities by the oncologists, timely information of the patients through verbal language and appropriate pamphlets, a good physician-patient communication, an appropriate application of supportive care protocols. All these elements should be included within multidisciplinary cooperation and in a standardized path including several medical professionals (medical oncologists, gastroenterologists, endocrinologist, general practitioners) with the aim of a short- and long-term evaluation of the oncological patients.
In Italy, some facilities have realized a multi-specialist dedicated team within the Oncology Units and data coming from these experiences highlight that this kind of approach determines a net reduction of unplanned hospitalizations and related costs. For such reasons in the last few years major attention has been drawn on this model, which is not focused on the cancer treatment, but on the cancer patient care (25-27).
Apart from the physicians, the involved health professionals are psychologists, spiritual assistants, and specialized nurses: some literature data show a possible positive impact on the management of toxicities through an *ad hoc* nurse intervention (28). The high specialized nurse professionals can apply an evidence-based care model, thus positively impacting the clinical outcome (29-31).
Integrated supportive care models that are proposed nowadays often deal with the most common side effects, as reported above. Still, there is a lack of randomized clinical trials that investigate the diverse supportive care modalities in the different new therapeutic settings, such as in the immunotherapy and targeted therapy setting. Such models should investigate how these new toxicities might determine a worsening of the quality of life and, then, an increase in the number of unplanned visits and hospital admissions, but also of the morbidity and the mortality.
All these things considered, major attention to the quality of life needs to have a higher offer of diagnostic and therapeutic paths with the use of one of the following modalities: either a closer hospital follow-up or the use of less invasive, home-based approaches. In the latter case, this could be performed through home visits or home phone calls. Furthermore, with major access to health information, the patient him- or herself might become a more active partner in his/her care path (1).
Specialised home assistance has been evaluated in patients undergoing oral chemotherapy. The programme consisted in home visits, 24/7 phone availability, and a weekly phone call and it has shown that the experimental group experienced a lower incidence of toxicities than the control group, but also a lower number of accesses to the reference hospital or other health facilities and a reduction of the number of days of hospital stay (28). Though positive, the results of this trial also showed increased costs. For such reasons, there are data that a phone-only nurse follow-up might be an alternative to answer to the patients'need with lower costs and thus it might determine a toxicity reduction when compared with standard monitoring (32-35).
The studies on the management of oral therapies show how fundamental it is that the involved nurses are highly specialised in the disease and trained to take immediate therapeutic decisions, such as the variation or the interruption of the treatment, through the use of pre-established and agreed protocols, that were previously shared with medical professionals (34). An educational programme on oral therapies might have the final aim of limiting the dose reductions and inadequate treatment withdrawals.
Another field of interest is the management of "acute events" that might happen between therapy cycles. Waiting for the subsequent cycle might cause a lack of reporting of some serious side event.

The vast majority of trials based on electronic monitoring evaluate the toxicities during planned visits (36-40). Only a few studies also included home control between hospital visits (through an interim phone call) (41-42). Even if data are contrasting, some data show that, by intensifying the treatment of toxicities and symptoms, the application of supportive care guidelines, as well as the training of the patient, might lead to a statistically and clinically reduction of the toxicity severity (42).
A systematic literature review on 50 studies showed that there are three types of distance interventions: treatment and side effect monitoring, but also phone-based follow up (rather than hospital follow up), and psycho-educational phone interventions (43).
In lots of studies there is a positive perception for this approach, which is not only effective and feasible, both for clinicians and patients, but also is a good way to guarantee easier access to care, especially for those patients who live far from the referral centres o in rural areas, when supportive care services are limited (42-45).
However, Liptropp revision (43) highlights contrasting results: the positive perception was reported in all three overmentioned settings, even if with higher magnitude in the field of adverse event management and treatment and in the psycho-educational settings, where phone calls are lived as an adjunct component to the standard care. The phone call is seen as an immediate source of reassurance and information, but also a continuum of care and it gives important support of emotional nature, whereas in the follow-up setting patients refer an important reassurance through physical examination and direct physician-patient relationship (43).
Another important aspect is to understand how much this method can influence medical management. Some data suggest that home management can reduce the re-hospitalization rate, since many health conditions could be treated at home, especially with good clinical surveillance (44); minor access to healthcare facilities, emergency room and general practitioners was observed (28; 34). Phone surveillance might also ease the passage from hospitalization to the outpatient setting and reduce the number of acute events (6; 45). However, further studies in this setting are needed.

NICSO trial includes the accrual of patients on adjuvant chemotherapy for breast, colon, and lung cancer, on targeted therapies or immunotherapy. It aims at evaluating the difference in terms of toxicity (but also Quality of Life, number of accesses to the emergency room, numb er of unplanned specialist visits, number of hospital admission and days of hospitalization) in patients who undergo a standard evaluation for prevention and treatment of toxicities compared to a group of patients who receive, apart from the standard evaluation, a periodical phone-based nurse monitoring.

To sum up, the lack of adherence to guidelines on prevention and treatment of the different toxicities induced by chemotherapy, targeted therapies, and immunotherapies is a reason for the possible increase in the incidence and duration of the same side effects.
There is a need for a precocious diagnosis of side effects in order to have better clinical management and a reduction of the intensity and duration of these events.
Better toxicity management can impact on the correct administration of cancer drugs (dose intensity).
It is still debated by the scientific community which is the best modality and evaluation tools to be used. In particular, the main questions are:

- Side effect reporting by physicians and/or patients;
- Role of nurses in the evaluation of side effects;
- The impact of the evaluation tools (frequency, executor) on the reduction of time spent with toxicity, their severity and the adherence to cancer treatment.

The recent Basch study (52) confirmed that patients that use patient-reported outcome (PRO-CTCAE) as an evaluation tool for toxicity rather than standard monitoring have a benefit in terms of overall survival. This evaluation has been conducted on a setting of metastatic patients on chemotherapy (50-52). There is then the need for randomized multicentric clinical trials in different therapeutic settings (chemotherapy, targeted therapies, immunotherapies) to evaluate the possible impact of a planned, continuative nurse monitoring of these patients.

Being proposed and sustained by the multidisciplinary NICSO (Italian Network of Supportive Care in Oncology) and having as a primary objective the improvement of toxicity management, based on the Italian law DM 17 December 2004, the study is a non-profit trial and it is a part of the health assistance in order to better the clinical practice.

2. OBJECTIVES

Primary: To evaluate the number of days patients spend with a grade 3 or higher toxicity (among those considered). The specific toxicities that are the object of evaluation are chosen among those that are clinically relevant and are more likely responsible for a reduction of treatment adherence and, then, a reduction of the benefit from such treatment.

Secondary:

- ✓ Incidence and duration of grade 1-2 toxicities;
- ✓ Number of emergency room accesses and unplanned specialist visits;
- ✓ Number of hospital admissions and days spent in the hospital because of treatment -related toxicities
- ✓ Evaluation of quality of life.

Exploratory:
Variation of the oncology treatment dosage (dose intensity).

3. STUDY DESIGN

Multicentric, randomized, open-label trial of comparison of planned, continuative nurse monitoring intervention together with an information sheet with advice about prevention and treatment of treatment-related toxicities – chemotherapy-, targeted therapy- or immunotherapy-related ones versus the exclusive use of the same information sheet.

3.1 Study population

Every patient with a solid tumour treated with adjuvant chemotherapy or targeted therapy or immunotherapy for metastatic disease will be included.
In the second and third group patients receiving either targeted therapies or immunotherapies will be eligible.

The following inclusion and exclusion criteria are valid for all groups:

Inclusion criteria

- Patients aged 18 or over.
- Histological diagnosis of solid tumour treated with the following drugs (defined per group):

- Adjuvant chemotherapy:
  - anthracyclines and cyclophosphamide ± taxanes (breast cancer)
  - oxaliplatin and fluoropyrimidines (colon cancer)
  - combination of platinum or its derivatives (lung cancer)
- Oral targeted therapy:
  - sunitinib, pazopanib (kidney cancer)
  - gefitinib, erlotinib,afatinib, crizotinib (lung cancer)
  - vemurafenib ± cobimetinib, dabrafenib ± trametinib (melanoma)
  - everolimus ± exemestane (breast cancer)
  - aromatase inhibitors + CDK4/6 inhibitors (breast cancer)
  - fulvestrant + CDK4/6 inhibitors (breast cancer)
  - vandetanib, lenvatinib (thyroid cancer)
  - vismodegib (cutaneous basal cell carcinoma)
  - imatinib (GIST)
- Immunotherapy:
  - anti-CTLA4 drugs,
  - anti-PD-1/PDL-1 drugs,
  - their combination.

- Written consent signature;
- Availability, and accessibility, for phone contact;
- Life expectancy ≥ 6 months.

Exclusion criteria:

- Presence of symptomatic brain metastases;
- Presence of neurological and psychiatric diseases or other conditions that may prevent patients from being compliant to protocol procedures;
- Prior exposure to systemic oncological treatment. This criterium is justified by the fact that having received a previous oncological treatment usually causes an alteration of the toxicity profile and in these cases, the attention to toxicity is higher and patients often receive other preventive treatments.
- Participation in other clinical trials.
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3.2 Patients'classification and randomisation

Eligible patients are split up into three subgroups according to the oncological treatment

- Patients on adjuvant chemotherapy
- Patients treated with oral targeted therapy for the first time
- Patients treated with immunotherapy for the first time

Within each subgroup patients are randomised to receive:

× a periodical nurse monitoring phone call, that is planned and agreed with the patient, together with an information sheet with advice about prevention and treatment of toxicities (Experimental group)

× an information sheet with advice about prevention and treatment of toxicities (Standard group).

1:1 randomisation will be performed via computer using the randomly permuted blocks system.

All participants are to give their written informed consent.

3.3 Study duration

The study will last 24 months. Patients'accrual will have a duration of 18 months, from the beginning of the trial. The study period will be 4 months for the immunotherapy and targeted therapy groups and 6 months for the adjuvant chemotherapy group.
The study can be interrupted earlier in case of oncological treatment discontinuation because of disease progression, unacceptable toxicity, or withdrawal of consent by the patient, or patient's death. In case of temporary suspension of the oncological treatment, patients will continue to be monitored according to the group they are assigned. The study ends with the end of the monitoring period, that is with the last phone call to the last enrolled patient.

4. OPERATIVE ASPECTS

The realisation of the study was preceded by a programme of training meetings about supportive therapies in patients receiving oncological treatments. These meetings were organized in the entire national territory. At least one oncologist in each of the 63 centres that have joined the trial participated in these meetings.
During these meetings, an information dashboard has been developed and shared. This dashboard, that is useful for both the physician and the patients, contains the best supportive therapy for every administered oncological treatment (according to the expected toxicities).
This dashboard was developed with the help of several health professionals (physicians and nurses) and the support of a board of specialists (dermatologists, gastroenterologists, cardiologists, endocrinologists). It is formed by a synthetic sheet that is customized according to the oncological treatment, based on the expected treatments.
This intervention, based on either national and international guidelines (AIOM, NCCN, MASCC, ASCO) is the standard for the prevention and treatment of therapy-related toxicities.
The study provides the randomisation between the use of the information sheet and the addition of a periodical nurse monitoring intervention that is planned and agreed with the physician. The nurse team that is in charge of the monitoring interventions is centralized (Nurse Operation Center) and is adequately trained about the potential toxicities that may come out during the study. The team has a function of coaching and training and supports the patient's empowerment (see Appendix 1 – Service guide).

The nurse monitoring intervention consists of a weekly phone call throughout the entire period of treatment and it follows a protocol of predefined and individualized questions in order to evaluate the toxicities according to the treatment group. During the empowerment phone call, the patient is encouraged to adopt the correct protocols for prevention and cure according to the specific oncological treatment.

The possible actions that may arise during the phone call (codified in the nurse algorithm) may be:

a) advice on the use of drugs and therapeutic/preventive actions according to the information dashboard;
b) facilitation of the contact of the patient with the referral specialists and/or general practitioner in case of toxicities that do not need an urgent intervention (within 12 hours);
c) in case of toxicities that need an urgent intervention (less than 12 hours): facilitation of the contact with the referral physician or, if the contact is not possible, suggestion to access to the hospital through the centre-specific modalities (access

to the emergency room, access to the supportive care service, and so on);
d) in case of not deferrable urgencies: direct access to the emergency room through the emergency services (118).

At the end of every phone call, the Nurse Operative Center gives a synthetic report of the detection and sends an appropriate email to the reference physicians (identified at the moment of randomisation).
During the evaluation period, according to the PRO-CTCAE (validated in Italian) (53) (Attachment 1, 2, 3), in both groups, a questionnaire for the monitoring of toxicities will be administered to each patient.
This questionnaire, which takes into consideration the previous week, monitors the frequency (F), severity (S), and intensity (I) of each symptom. A question about the number of days spent with toxicity will be performed. The administration of the questionnaire will be made through a pre-registered phone call (without an operator), which is based on an electronic score coding. This phone call does not overlap with the monitoring phone call in the specific randomisation group.

For the patients'privacy, every date coming from the project will be dealt with according to the current laws.

In each group, at the baseline visit, then every month, the EORTC QLQ-C30 questionnaire (Attachment 4) will be administered.

In both groups, there will be a monitoring activity of the number of unplanned hospital accesses (emergency room or specialist visits). An evaluation of the number of hospital admissions and days of hospital stay (due to toxicities) will be performed.

Finally, the dose intensity of the oncological drugs throughout the period of treatment will be monitored (it will be considered as the ratio between the administered dose and the planned dose). This aspect is fundamental not only for the management of the oncological therapy but also for the adherence to the recommendations of supportive care.

5. STATISTICS

5.1 Sample size

The recent events related to the COVID19 pandemics have slowed down the accrual of the study. For this reason, a revision of the sample size has been necessary.
The revision only involves group B and C, since the accrual of group A was completed according to the original version of the protocol.

Group A
Considering the lack of data from the literature about the duration of side effects, especially grade 3 and 4, but estimating a prevalence of about 15%, considering a power of 0.9 and an alpha value of 0.05, it is then necessary to have 207 patients for each arm of the study to show a reduction from 15% to 5% of the proportion of days spent with a grade 3 or higher toxicity.

Groups B and C
Considering the same lack of data, but estimating a prevalence of about 25%, considering a power of 0.72 and an alpha value of 0.05, it is then necessary to have 50 patients per

arm per group to show a reduction from 25% to 5% of the proportion of days spent with a grade 3 or higher toxicity.

The entire sample size is then formed by 614 patients, to be found among the 63 involved centres.

5.2 Data management

The investigator of each centre, together with the designated personnel, is in charge of the report of the required information through the specific electronic case report form (eCRF), that is provided by the Promotor. Data collected in the eCRF are anonymous and the patient will be identified only through a specific code. All the data are elaborated and analysed by the study scientific committee. All data are archived anonymously according to the guidelines for the treatment of personal data in clinical trials (Italian law approved on 24th July 2008, Official Gazette of 14th August 2008). Genetic data are treated according to the authorization 8/2013 (general authorization on the treatment of genetic data). The access to these data is protected by the investigator of each centre.

5.3 Data analysis

Qualitative variables are synthesized in absolute frequencies and percentages; quantitative ones through mean and standard deviation, maximum and minimum, median and interquartile range. The evaluation of the statistical significance of the differences between two main groups (nurse monitoring vs standard monitoring) will be analyzed through the Student's t-test for dependent groups in case of quantitative parameters. The chi-square test will be used to evaluate the statistical significance of the differences in qualitative parameters. The comparisons among groups will be performed at the end of the study. The statistical significance of the variations in time of quantitative variables will be performed through the two-way analysis of variance (ANOVA). A secondary analysis will be performed, aiming at evaluating the statistical significance of the differences in all the other parameters between the two groups.

6. PHARMACOVIGILANCE

6.1 Legislation

Since this study aims at the evaluation and the improvement of the prevention and treatment of toxicities of oncological treatments, here we present the main definitions according to the European legislation on pharmacovigilance – that is a reference for the Italian legislation. This legislation was modified by the entry into force of the EU Regulation n. 1235/2010, whose application has been operative since the 2nd of July 2012, and the Directive 2010/84/EU, that is currently being implemented. Based on these legislations, pharmacovigilance is defined as "the complex of activities that aim at continuously evaluating all the information related to drug safety and at ensuring a favourable benefit/risk ratio for the population for all the drugs on the market". The definition of adverse reaction has been changed and it is now considered as a "noxious and unintended effect related to the use of a drug". This definition considered, all adverse events will be notified, also those that are related to therapy error, abuse, misuse, off label use, overdose, or professional exposure.

6.2 Adverse event report: investigators' responsibilities

During the study, the overmentioned pharmacovigilance legislation will be respected. Investigators in each centre will be then asked to respect the current legislation and will be

in charge of reporting all adverse events related to the use of the drugs that are monitored in the study. The reporting will be notified to the local health authority, or the responsible for pharmacovigilance of the healthcare facility, through the sending of a copy of the "Form for the Reporting of Suspected Adverse Event".
It is important to specify that all adverse events happening in the subjects included in the study during the study period will be recorded by the investigators in the eCFR.
We then report some definition and some evaluation criteria.

6.2.1 Adverse reaction (AR)

According to the current legislation, an AR is defined as every unintended medical event that happens in a patient or subject included in the clinical trial who is receiving a drug; this event is not necessarily in a causal relationship with the used drug. Examples of AR include (but are not limited to):
- abnormal results of laboratory tests,
- clinically relevant signs and symptoms,
- hypersensitivity,
- progression/worsening of the disease.

Furthermore, they can include signs and symptoms that may come from:
- drug overdose;
- treatment discontinuation;
- drug abuse;
- incorrect use of drugs;
- drug interactions;
- drug addiction;
- uterine exposure.

6.2.2 Severity evaluation

AR severity will be evaluated according to the NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events), version 4.03 (see Appendix 1 – Medical Dashboard).

A brief definition is reported to clarify the meaning of each term.
Grades: Grade refers to adverse event severity. CTCAE is based on a scale from 1 to 5:

- Grade 1 – mild: asymptomatic or mild symptoms; only clinical or *imaging* follow up is required; no need for specific intervention;
- Grade 2 – moderate: minimal and non-invasive intervention is required; the event determines a slight limitation in the instrumental daily activities;
- Grade 3 – severe: clinically significant, but not immediately dangerous for life; hospitalisation or prolongation of hospital stay is needed; disabling; it causes a limitation of the daily activities that are related to the person's self-care;
- Grade 4: potentially fatal consequences; urgent intervention is needed;
- Grade 5: adverse event-related death.
-

Since not all the grades are appropriate for all the AR, in case of AR which does not relate to an appropriate NCI-CTCAE grading, the usual severity classes are used: mild, moderate, severe, potentially fatal, and fatal. These are defined as follows:

GRADE	Description

Mild	It does not interfere with the subject's daily functional activities
Moderate	It interferes with some of the subject's daily functional activities
Severe	It significantly interferes with the subject's daily functional activities
Not evaluable	There is insufficient or incomplete evidence to perform a clinical evaluation of the causal relationship

6.2.3 Casuality evaluation

The causality evaluation by the investigator should be performed for every adverse event. The investigator's evaluation is the determination of whether there may be a reasonable possibility that the monitored pharmacological treatments may have caused or contributed to the adverse event. To give conformity of judgement, the evaluation should be defined as follows:

CAUSALITY	Description
Not related	There is no evidence in support of the drug-event relation
Improbable	The evidence that suggests a causality relation is scarce and not very sustainable (e.g. the event does not happen with a reasonable time from the drug administration). Other reasonable causes may explain the event (e.g. the patient's clinical conditions; other concomitant treatments)
Possible	There is some evidence that suggests a causal relationship (e.g. the event happens within a reasonable time from the drug administration). However, the presence of other conditions may contribute to the event (e.g. the patient's clinical conditions; other concomitant treatments)
Probable	There is evidence that suggests a causal relationship and the influence of other factors is improbable
Certain	There is evidence to support a causal relationship and the influence of other factors can be excluded
Not evaluable	There is no adequate evidence or evidence is not complete to perform a clinical evaluation of the causality relationship

All the adverse events happening during the study will be recorded in the eCRF.

7. ETHIC ASPECTS

The study will be conducted according to the protocol, following the principles of the Helsinki Declaration (last revision of October 2013), the rules of the Good Clinical Practice (ICH GCP), the laws on data protection and other applicable regulations, including the pharmacovigilance laws and the Good Pharmacovigilance Practice, which is a reference for the realisation of this type of studies.

8. DIRECT ACCESS TO DATA AND ORIGINAL DOCUMENTS

Unless requested by law, only the investigator and his/her staff, the Ethics Committees, the Monitors, the Study Coordinators, the Auditors and the inspectors from governmental bodies may directly access to the archives to connect the study data with the single patients. In particular cases, such as the inspection by regulatory agencies, the information of each patient, report anonymously in the eCRF, may be connected to his/her clinical data through

the appropriate key (which is kept by the investigators).

9. DATA PUBLISHING

There are no constraints to data publishing. The promoter takes the responsibility to share the results with the investigators from the participating centres (see Appendix 2) and, on behalf of the entire working group, to publish them or to make them public during scientific congresses, symposia, and so on.

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