Study protocol

Research study: Tattooing of skin set-up markings in Radiotherapy: comparison between the traditional system and the Comfort Marker 2.0®

Abbreviated Study Title: COMFORTATTOO

Version 3.0 of 10/4/2021

The COMFORTATTOO trial has been approved by the IPO-Porto ethics committee.

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Background

Most radiotherapy (RT) treatments performed nowadays rely on conformational techniques that encompass the use of a computed tomography (CT) as part of the planning workflow. In this process, a three-dimensional image, generally known as CT simulation, is obtained in the planning position, using positioning supports and immobilization systems. In selected cases, one of the steps after acquiring the CT simulation is the realization of reference markings on the skin of the patient, that are tattooed at defined points, using a laser system. These markings must remain on the patient's skin in a visible, clear, and unambiguous way, to guarantee a reproducible positioning in the linear accelerator in all fractions of the treatment. The location of the set-up markings is variable, depending on the anatomical area to be treated, and is defined in service protocols.

Currently, at the External Radiotherapy service of the IPO in Porto, set-up marking is performed using disposable lancets (produced primarily for capillary blood sample collection) and India ink. Since it is not possible to regulate the depth of pigment application according to the thickness of the skin of each patient, it is a process that is typically accompanied by discomfort or transient pain for the patient, in addition to which the markings remain visible on the skin for several years old.

To circumvent these limitations, the *Comfort Marker* 2.0® emerged, developed by CIVCO® *Medical Precision*. The device was designed to tattoo set-up markings with controlled and adjustable depth applications. As potential benefits, this feature may translate into less pain for the patient compared to the traditional system, with the benefit of potentiating earlier fading of the ink, with cosmetic advantages.

The present study aims to compare the two systems of cutaneous reference point tattooing: the lancet-based system (hereinafter referred to as the traditional system) and the *Comfort Marker* 2.0® system.

Identification of the research study

Full title: Tattooing of skin set-up markings in Radiotherapy: comparison between the traditional system and the Comfort Marker 2.0®

Short Title: comfoRTattoo

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Number of investigation sites: One

Number of participants included planned: 100

General information of the research study

Study design: single-center, experimental, prospective, longitudinal, parallel with 2 groups (1:1), randomized, *double-blinded*

Statistical considerations: Eligible patients will be randomized via computer-generated random permuted blocks (block sizes of 10), stratified by the number of set-up markings (≤ 4 vs. >4), to one of two possible groups. To guarantee the concealment of the attribution, a computer-generated list will be prepared by a person external to the study, which will serve for the preparation of closed white envelopes, of the same size, sequentially numbered, opaque and sealed, which will be distributed by the principal investigator to the TC simulation technicians.

Objectives: To compare two set-up tattooing systems: lancet-based vs. *Comfort Marker* 2.0® system.

Inclusion criteria:

1. Patients referred to the External Radiotherapy Service for external beam RT;
2. Patients in need of set-up markings as an inherent part of the Radiotherapy process;
3. Age ≥18 years at the date of the first radiation oncology consultation;
4. Good *performance status* (ECOG PS 0-1)
5. RT treatments with an estimated fractionating schedule of ≥13 once-daily fractions;
6. The signing of informed consent.

Exclusion criteria:

1. Patients requiring either immobilization thermoplastic masks (for head or head and shoulders) or vacuum cushion
2. Patients referred to the external radiotherapy service under an inter-hospital protocol.

Criteria to be evaluated :

1. Patients' comfort (Pain inherent to the tattoo procedure);
2. Radiation therapists' satisfaction (Evaluation of the ease of application of the markings);
3. **Effectiveness (**set-up markings visibility across RT fractions);
4. Fading across RT fractions;
5. Fading at 6 months after tattoo application;
6. inadvertent sharps injuries.

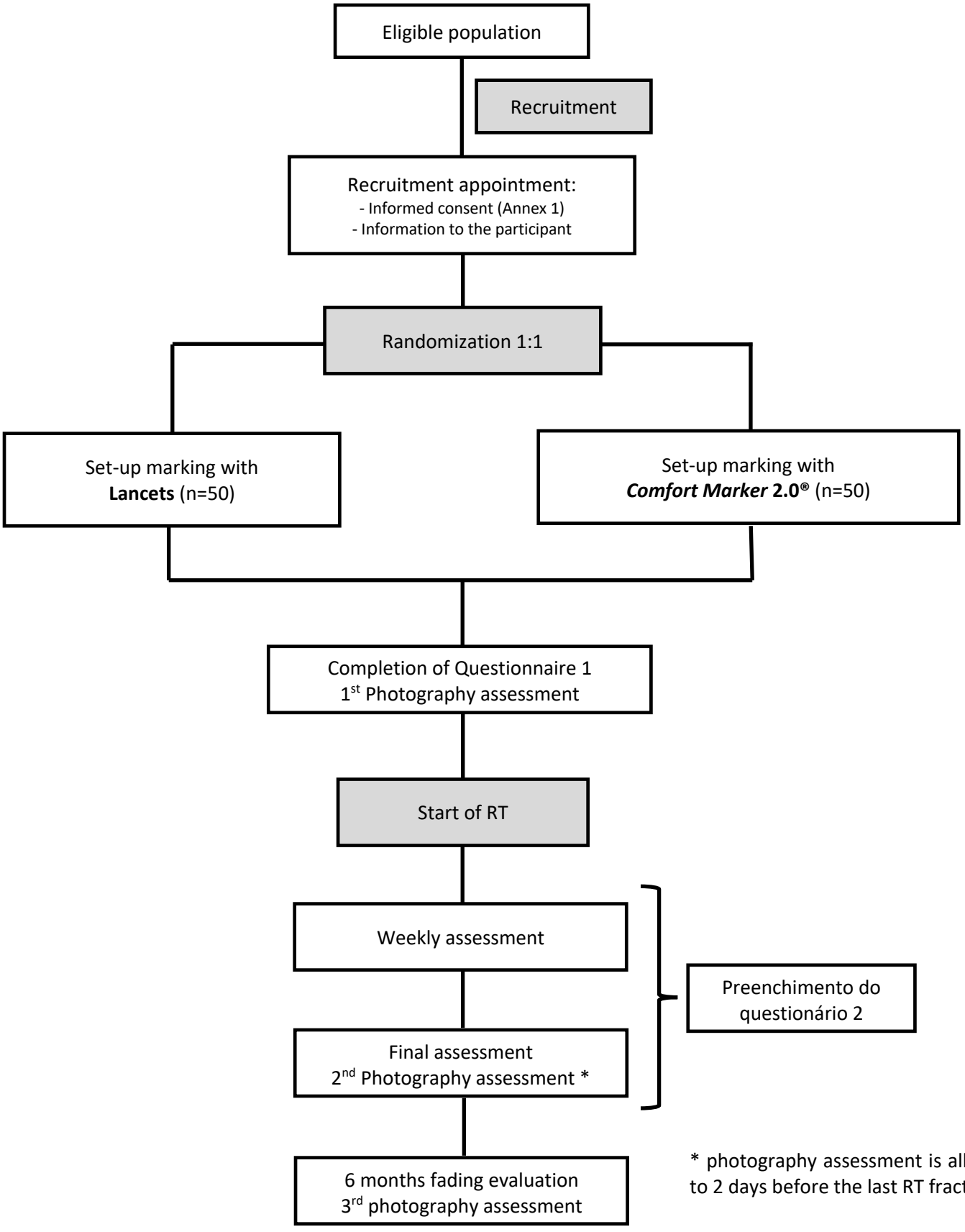
Considerations for *Comfort Marker 2.0* ®

The *Comfort Marker 2.0*® device consists of a Control Unit and a Pen Module, the latter being responsible for activating the marking needle.

Safety Needle, Ink Cup, Pigment

For the present study, the *Comfort Marker 2.0* ® system will be transferred to the Portuguese Institute of Oncology in Porto, free of charge, without any charges. This will consist of 1 *Medical Precision Comfort Marker 2.0* (consisting of the control unit and its Pen) and 1 *Medical Precision Patient Marking Set* (which includes: 50 needles, 50 pigments, and 50 pigment containers).

Study planning:



* photography assessment is allowed up to 2 days before the last RT fraction

Attachments

Informed consent for the investigation

Considering the "Declaration of Helsinki" of the World Medical Association (Helsinki 1964; Tokyo 1975; Venice 1983; Hong Kong 1989; Somerset West 1996; Edinburgh 2000; Washington 2002, Tokyo 2004 and Seoul, 2008)

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I, the undersigned (full name of adult person or volunteer) _____

_____

have received the Participant Information text regarding the procedure I agreed to perform. I understood the explanation given to me by the researcher signing this document. I was also given an opportunity to ask such questions as I thought necessary, and to all of them I received a satisfactory answer.

I have learned that, per the recommendations of the Declaration of Helsinki, the information or explanation provided to me covered the objectives, methods, expected benefits, potential risks, and possible discomfort. Furthermore, I was told that I have the right to cancel my participation in the study at any time, without this having the effect of having any effect on the assistance provided to me.

Therefore, I consent to the method, treatment, or survey proposed by the researcher being applied to me.

Signature of the person or volunteer:_____Date:___/___/202_

I confirm that I have explained to the person indicated above, in an adequate and intelligible manner, the procedures necessary for the activities referred to in this document. I answered all the questions that were put to me and made sure that there was a sufficient period of reflection to make the decision. I also guaranteed that, in case of refusal, the best possible care will be ensured in that context, with respect for their rights.

Legible name of the Investigator in charge: _____

Signature of the Investigator in charge:_____Date:___/___/202_

Annulment of Informed Consent

I declare that I have received the Information to the Participant regarding the study/research project in question, which was proposed to me by the researcher who signs this document and **I intend to withdraw** the consent given on the date ____/____/202___.

Signature of the person or volunteer are: _____ Date:___/___/202_

Signature of the Responsible Investigator: _____ Date:___/___/202_

Note: This document is made in two copies - mandatory supply of a copy to the participant

Ethics Committee for Health of the Portuguese Institute of Oncology of Porto Francisco Gentil, E.P.E. (Doc. CES-IPOP 04)_2017

Annex 1: Informed Consent

INFORMATION TO PARTICIPANT

Dear Sir/Madam,

I would like to invite you to participate in the study "Tattooing of skin set-up markings in Radiotherapy: comparison between the traditional system and the Comfort Marker 2.0®", to be carried out at the External Radiotherapy Department of IPO-Porto by Dr. André Luís Miranda Pires, resident in Radiation Oncology.

The aim of the study is to compare two set-up marking systems, namely the traditional system (which uses lancets and India-ink) and the Comfort Marker 2.0® system (which uses an electrical device with an adjustable tattoo pen), to assess differences in terms of effectiveness, pain, fading and safety for the technical team. Your participation is very important and consists of: 1) tattooing the reference points (necessary to carry out the radiotherapy treatments) when performing the simulation computed tomography by one of the two methods previously presented; 2) filling in a questionnaire to assess pain/discomfort; 3) assessing the fading of the benchmarks after 6 months; 4) and making a photograph registry of the tattoos. If you choose to participate, you will be randomly selected by a computer to receive one of the tattoo methods. We do not anticipate risks from your participation in this study, nor will it translate into an increase in terms of exams or visits to the institution where it takes place.

We clarify that participation in the study is completely voluntary, and you can ponder on the decision to participate, including consulting family members if deemed necessary. At any time, you can withdraw, without having to justify and without prejudice to the relationship with the doctor and other health professionals. The information will only be used for the purposes of this research and for the publication of scientific articles, being treated with the utmost secrecy and confidentiality, to preserve personal data, in accordance with the legislation in force. The participants in the study declare that there are no conflicts of interest. We also clarify that there is no economic value to be received or paid for your participation. This study was approved by the Ethics Committee and the Data Protection Officer of the IPO-Porto.

Any questions or if you need further clarification, you can contact the responsible researcher, Dr. André Miranda Pires (email: i2489@ipoporto.min-saude.pt) or the Data Protection Officer of the Portuguese Institute of Oncology of Porto Francisco Gentil, who was aware of the approval of the study (email: epd@ipoporto.min-saude .pt). For more information about your privacy rights, you can contact the National Data Protection Commission, via email geral@cnpd.pt, by phone +351 213928400 or by writing to the following address: Av. D. Carlos I, 134 - 1.º, 1200-651 Lisbon.

Ethics Committee for Health of the Portuguese Institute of Oncology of Porto Francisco Gentil, E.P.E. (Doc. CES-IPOP 02)

Annex 2: Information to the participant

Questionnaire 1

Research study: Tattooing of skin set-up markings in Radiotherapy: comparison between the traditional system and the Comfort Marker 2.0®

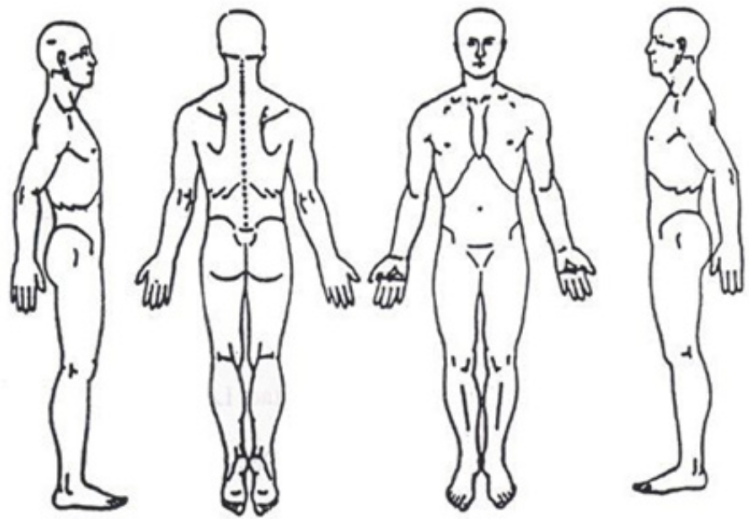
Patient ID

1. Randomization Arm: ☐ Lancets ☐ Comfort Marker 2.0

2. Set-up Markings:

2.1. Number of markings tattooed:

2.2. Localization (identify in the figure with sequential numbering):



Nr	Depth (mm)	Nr	Depth (mm)
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

3. Inadvertent sharps injuries.: ☐ Yes ☐ No

If yes, explain the event.

4. Assessment of the ease of tattooing: ☐ Easy ☐ Medium ☐ Hard

5. **Patient-reported pain assessment**:

0 – none 10 - worst imaginable pain

If more than one reference mark is made, assign an overall score.

0	1	2	3	4	5	6	7	8	9	10

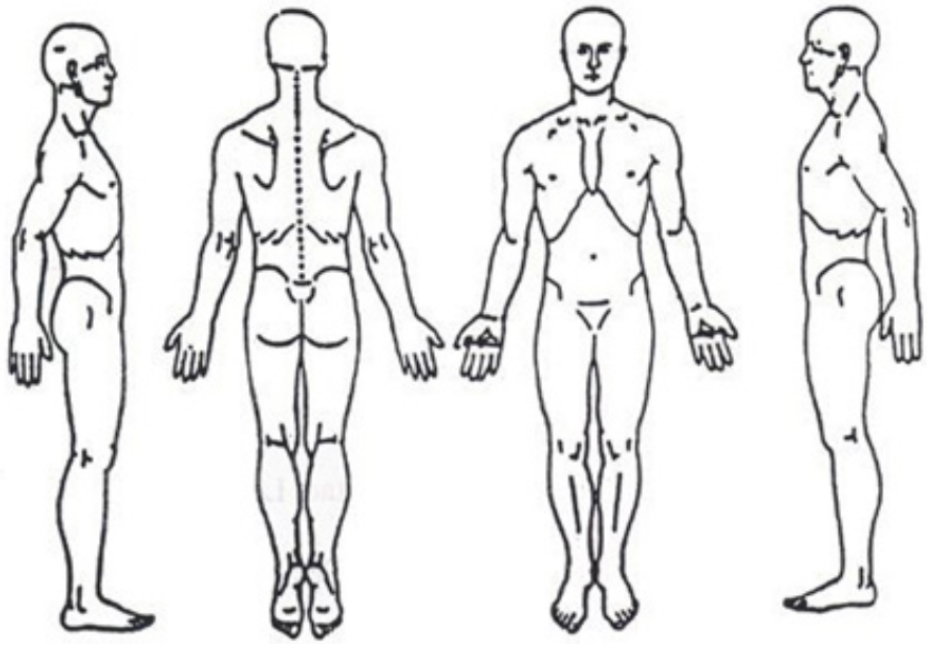
Date: ___/____/_____ Signature:_____ Mec. number:_____

Annex 3: Questionnaire 1

Questionnaire 2

Research study: Tattooing of skin set-up markings in Radiotherapy: comparison between the traditional system and the Comfort Marker 2.0®

Patient ID



1. Quality assessment of the patient set-up markings:

Note: Perform the assessment for EACH set-up marking.

Nr of tattoo	Data	Quality				Evaluator (Mec. nr)
		Bad	Reasonable	Good	Very Good	
1						
2						
3						
4						
5						
6						
7						
8						

Annex 4: Questionnaire 2 (in Portuguese)