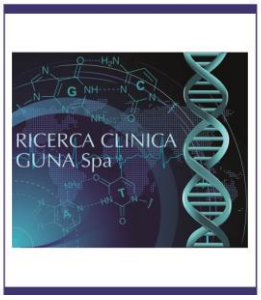

Centro Specialistico Ortopedico Traumatologico
Gaetano Pini-CTO

Sistema Socio Sanitario
Regione Lombardia
ASST Gaetano Pini

CLINICAL INVESTIGATION PLAN CONCERNING THE MEDICAL DEVICE

"ROPIRAMED"

TITLE: EVALUATION OF THE PERFORMANCE AND SAFETY OF AN MD-SHOULDER COLLAGEN TYPE I MEDICAL DEVICE IN THE TREATMENT OF ROTATOR CUFF SYNDROME.''ROPIRAMED PILOT STUDY

IDENTIFICATION CODE:	MDG2021184
EUDRACT:	NA
CLINICAL INVESTIGATION PLAN VERSION AND DATE:	n° 3.0 del 15 Settembre 2021
NUMERO DI PAGINE	n° 26

INDEX

1. SYNOPSIS

TITLE	Evaluation of the performance and safety of a type I collagen medical device (MD Shoulder Collagen Medical Device) in the treatment of rotator cuff syndrome.''*Ropiramed pilot study*''
STUDY DESCRIPTION	This single-centre pilot clinical investigation will be based on a one-sample design. Variables will be assessed at 6 different times: at baseline (day 0), after weeks 2, weeks 4, months 3, months 6 and after months 12 i.e. 11 months after the end of the infiltrative treatment.
OBJECTIVES	The objective of this study is to evaluate, the performance of an intra-articular treatment with a collagen-based medical device in recovering joint function and reducing associated pain. The safety of the treatment will also be evaluated.
PRIMARY ENDPOINT	The primary End Point will consist of evaluating, by means of the Constant-Murley Functional Scale (CMS), the effectiveness, in terms of performance, of the MD-Shoulder *Collagen Medical Device* in recovering joint function and reducing pain associated with time T3 months. An increase of at least 13 points on the CMS scale is considered clinically significant.
POPULATIONS	A total of 24 subjects suffering from rotator cuff syndrome will be enrolled.
SELECTION CRITERIA	Inclusion Criteria: • Subjects aged > 18 years. • Subjects with shoulder pain for at least 3 month. • Subjects with a diagnosis of rotator cuff tendinopathy, subacromial conflict syndrome, partial rotator cuff tendon lesions (lesions A and B according to Snyder's Classification). • Subjects with a CMS score between 40 and 75. • Subjects who understood and signed the Informed Consent to Active Participation in the study. • Subjects capable of understanding the terms of the study and participating throughout. Exclusion Criteria:

	• Subjects with complete rotator cuff lesions (C lesions according to Snyder's classification). • Subjects with shoulder instability. • Subjects with adhesive retractile capsulitis. • Subjects undergoing HA and/or cortisone infiltration in a period < 3 months. • Subjects with diabetes mellitus. • Subjects with uncontrolled thyroid disease. • Subjects with coagulopathies. • Subjects on chronic treatment with immunosuppressants. • Persons with an allergy to porcine collagen. • Subjects who are pregnant or breastfeeding.
STUDY PHASE	Fase IV post market
NUMBER OF CENTRES	1 Experimental Center.
DESCRIPTION OF THE MEDICAL DEVICE UNDER STUDY	MD-Shoulder *Collagen Medical Device* is an injectable medical device based on porcine collagen type I; the collagen content is 100µg/2mL.
STUDY DURATION	The total duration of the Clinical Investigation will be 16 months. There will be a 4-month subject selection and recruitment period and a 12-month treatment and observation period.
STUDY DURATION PER SUBJECT	The duration of the study for each subject will be 12 months.

1. LIST OF ABBREVIATIONS

AE	Adverse Event
ASES	American Shoulder and Elbow Surgeons
CMS	Constant-Murley Score
COL-1	Collagen type I
E-CRF	electronic Case Report Forms
NSAIDs	Non-steroidal anti-inflammatory drugs
GCP	Good clinical practice
HA	Hyaluronic Acid
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MD	Medical Device
NRS	Numeric Rating Scale
MR	Magnetic resonance
ROM	Range of Motion
RCS	Rotator Cuff Syndrome
SAE	Evento Avverso Serio
SST	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

2. INTRODUCTION

2.1 Anatomical background on the rotator cuff

The rotator cuff is an anatomical structure consisting of the tendons of four muscles that originate at the level of the scapula and insert on the proximal humerus, these deep muscles of the shoulder: supraspinatus, subspinatus, subscapularis, and the small round provides rotational movements to the shoulder [1]. The supraspinatus muscle originates from the supraspinous fossa of the scapula to insert on the upper face of the trochis and together with the deltoid, acts as the motor muscle of scapulohumeral abduction. The supraspinatus muscle holds the head of the humerus against the glenoid cavity, preventing upward dislocation of the head of the humerus otherwise caused by the action of the deltoid [2]. The subspinatus muscle, external rotator of the shoulder, originates from the subspinous fossa of the scapula and inserts on the postero-superior aspect of the trochitis. The subscapularis muscle, internal rotator of the shoulder, originates from the scapular fossa and inserts on the trochine. Finally, the small round muscle, external rotator of the shoulder, originates from the inferior part of the subspinous fossa and inserts on the postero-inferior face of the trochis. This muscle complex has the important role of stabilizing the glenohumeral joint and counteracting the luxating action of the deltoid. By contracting, in fact, these muscles produce a downward force that perfectly opposes the opposite action of the deltoid, creating a rotational torque generating abduction (ivi). All four rotator cuff muscles join the scapula to the humerus, enveloping the glenohumeral joint; their tendons cover the capsule and fuse with it, playing an important role in preserving joint integrity [3]. These muscles are also referred to as transverse stabilizers of the shoulder because, through them, the head of the humerus is stabilized and maintained on the glans of the scapula.

2.2 Tendinopathy and rotator cuff injuries

Rotator cuff tendinopathy is a commonly encountered musculoskeletal disorder in clinical practice, with an incidence ranging from 0.3% to 5.5%, and an annual prevalence of 0.5% to 7.4% [4]. Furthermore, over time, at a monthly rate of 0.26%, this condition can progress to complete rotator cuff tendon injury resulting in worsening pain and shoulder function [5].

The etiology of rotator cuff tendinopathy is still controversial. Some authors believe that it is an expression of a primary extrinsic compression due to a reduction of the sub-acromial space, while others attribute this pathology to an intrinsic degeneration of the tendons with a consequent development of secondary impingement. In this case, the hypothesis is that an altered microcirculation of the shoulder tendons leads to weakness of the rotator cuff resulting in rising humeral head and compression of the overlying structures. What we do know is that in tendinopathies there are histologic changes in the structure of the tendons, which include increased glycosaminoglycans and proteoglycans content, remodeling of collagen fibers, hypercellularity, neovascularization, and changes in the extracellular matrix pattern with increased noncollagenous components. These cellular

and molecular alterations result in a change in the mechanical properties of tendons and lead to a chronic, often disabling pain condition [6].

Although conservative therapy should still be considered the first choice in cuff tendinopathy, the clinical results of the various types of nonsurgical treatments are still mixed and often show poor efficacy.

Numerous studies identify exercise as the most viable therapeutic option in the treatment of rotator cuff tendinopathy, although the amount and type of potentially optimal exercise has not yet been defined. In addition, physiotherapy does not seem to be able to change the natural history of this pathology.

This explains the growing interest of the scientific community in developing new biological therapies that can both improve shoulder function and promote tendon healing.

Among the most studied biologic therapies in rotator cuff tendinopathies, platelet-derived growth factors (Platelet-rich Plasma, PRP) appear to be the most widely used in clinical practice because they are easy to prepare, yet they present mixed clinical results. In contrast, mesenchymal stem cells have shown promising results, especially in vitro, but require invasive harvesting systems and the need to expand the cells ex vivo before they can be injected at the site of tendon injury. [7]

2.3 Pre-clinical studies

Recently, F. Randelli et al. studied the in vitro effects on tenocytes induced by MD-Tissue Collagen Medical Device, an injectable, ready-to-use, porcine collagen-based medical device (100 g/2 mL vials) [8].

In vitro results appear to demonstrate that *MD-Tissue Collagen Medical Device* can induce tenocyte proliferation and migration and type I collagen synthesis, maturation, and secretion, promoting tendon repair. [8]

F. Randelli et al. also demonstrated the purely mechanical activity of *MD-Tissue Collagen Medical Device*, which is able to induce changes in the morpho-functional properties of tenocytes. [9]

The aim of our study is to evaluate, by means of the Constant & Murley functional scale [Constant-Murley Score (CMS)], the performance of intra-articular treatment with a collagen-based medical device (*MD-Shoulder Collagen Medical Device*) in recovering joint function and reducing pain in rotator cuff tendinopathy.

3. SCIENTIFIC REQUIREMENTS

3.1 Study title

Evaluation of the performance and safety of a type I collagen medical device (MD-Shoulder *Collagen Medical Device*) in the treatment of rotator cuff syndrome.*''Ropiramed pilot study''*

3.2 Purpose of the clinical study

The purpose of this clinical study is to evaluate, through the CMS functional scale, the performance of intra-articular treatment with a collagen-based medical device in recovering joint function and reducing associated pain. The safety of the treatment will also be evaluated

3.3 Clinical study Design

This single-center pilot Study Clinical Investigation will be based on a One sample design. Variables will be assessed at 6 different times: at baseline (T0 time), after 2 weeks (T2w), after 4 weeks (T4w), after 3 months (T3months), after 6 months (T6/FU), and after 12 months (T12/FU) i.e., 11 months after the end of infiltrative treatment.

3.4 Duration of the Clinical Study

The total duration of the clinical study will be 16 months. There will be a subject selection and recruitment period of 4 months and a treatment and observation period of 12 months. (See Figure 1).

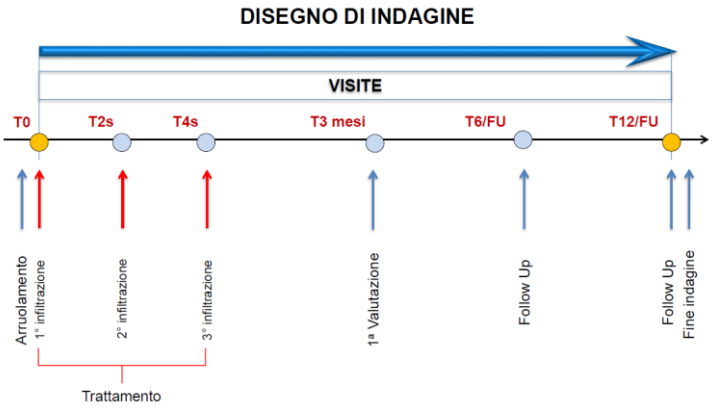

Fig.1 Flow chart of the clinical study design

3.5 Participating population

A total of 24 subjects with painful shoulder in rotator cuff tendinopathy will be enrolled. The recruitment phase will be closed no earlier than the number of subjects stipulated in the Clinical Investigation Plan has been reached.

Only subjects will be included:

- belonging to the U.O.C. 1st Orthopedic Clinic (Gaetano Pini Orthopedic Institute, Milan, Italy);
- who meet the inclusion criteria and have no exclusion criteria.

3.6 Enrollment

Enrollment will begin only after approval of the Clinical Investigation Plan by the ASST Istituto Ortopedico Gaetano Pini Ethics Committee and notification of the study at the Ministry of Health.
Enrollment will involve subjects with rotator cuff syndrome who are eligible according to the selection criteria. Diagnosis will be performed by the Principal Investigator through clinical examination and instrumental investigation with shoulder MRI. The MRI examination must be recent and of good quality; if the subject does not have it, an MRI examination will be performed before diagnosis and enrollment. Eligible subjects will be explained by the Co-Investigator the rationale for the Clinical Investigation Plan and the procedures involved. Consent to participate in the study will then be sought.

3.6.1 Selection Criteria

3.6.2 Inclusion Criteria

- Subjects with age > 18 years;
- Subjects with shoulder pain for at least 3 month;
- Subjects with a diagnosis of rotator cuff tendinopathy, subacromial conflict syndrome, partial rotator cuff tendon injuries (injuries A and B according to Snyder's Classification);
- Subjects with a CMS score between 40 and 75;
- Subjects who understood and signed the informed consent for active participation in the study;
- Subjects who are able to understand the conditions of the study and take part throughout the duration of the study.

3.6.3 Exclusion Critera

- Subjects with complete rotator cuff injuries (C injuries according to Snyder's classification);
- Subjects with shoulder instability;
- Subjects with adhesive retractile capsulitis;
- Subjects undergoing HA and/or cortisone infiltration in a period < 3 months;
- Subjects with diabetes mellitus;
- Subjects with uncontrolled thyroid disease;
- Subjects with coagulopathies;
- Subjects on chronic treatment with immunosuppressants;
- Subjects with allergy to porcine collagen;
- Subjects in pregnancy or lactation.

3.7 Subjects Coding

At the time of enrollment, each subject will be assigned a complex alphanumeric identification code formed by the progressive enrollment number followed by an alphanumeric code generated by GUNA S.p.a. through Random Sequence Generator (www.random.org.).

The complex code is found to be in compliance with the current Privacy Regulations regarding coding of subjects participating in clinical trials.

4.9 Procedures

4.9.1 Timing of Evaluation

T0 baseline: Enrollment and start of infiltrative treatment.

T2 weeks: Second infiltrative treatment.

T4 weeks: Third infiltrative treatment.

T3 months: Visit 1st Evaluation.

T6 months/FU: Follow-up visit.

T12 months/FU: Follow-up visit.

4.9.2 Plan Visits

T0 BASAL: Enrollment

During the daily clinical activity, investigators participating in the Investigation will select subjects with rotator cuff syndrome. The Principal Investigator will be responsible for the correct clinical diagnosis by also making use of the instrumental examinations provided in the Investigation Plan. Subjects meeting the selection criteria will thus be identified. After fully explaining the purposes, aims and procedures stipulated in the Clinical Investigation Plan, the subject will be offered participation in the Clinical Investigation Plan itself. Finally, the selected subject will be asked to review the information form and to date and sign the Informed Consent and Consent to Processing of Personal Data form.

Female subjects will need to provide evidence of a negative pregnancy test in order to be enrolled.

We will then proceed with the objective examination and collection of the information required by the appropriately prepared Electronic Data Collection Form.

This will be followed by:

- CMS assessment;
- NRS assessment;
- ASES assessment.
- SST evaluation;
- shoulder ROM evaluation;
- MRI evaluation.

The first infiltration will then be performed via ultrasound.

Previous or ongoing pharmacological treatments of any kind will be documented.

In order to monitor the consumption of analgesic (Celecoxib 200mg / Paracetamol 1000 mg) used during the Clinical study in case of pain onset, a clinical diary will be given to the subject in which to indicate the day and dose of medication used.

The enrolled subject will be given the identification code formed by the progressive enrollment number followed by an alphanumeric code.

T2 week (±2 days):

At 14 days from day 0 (enrollment), the second infiltration will be performed through echoguide and pain assessment through NRS, finally painkiller drug use will be evaluated through clinical diary analysis, and any Adverse Events occurred after the first administration will be assessed.

T4 weeks (±2 days):

At 28 days from day 0 (T4w), the third ultrasound-guided infiltration and pain assessment through NRS will be performed, finally painkiller drug use will be assessed through clinical diary analysis and any Adverse Events occurred after the last administration will be evaluated.

T3 months (±7 days):

At 3 months from day 0 and at 2 months from the last echoguided administration, the End Points in the Clinical Investigation Plan will be assessed.

Including:

- CMS assessment;
- NRS assessment;
- ASES assessment.
- SST assessment;
- shoulder ROM assessment;
- assessment of pain killer drug consumption used in case of pain onset through clinical diary;
- evaluation of any Adverse Events.

T6/FU (±7days):

At 6 months from day 0, we will again proceed with the assessment of the End Points stipulated in the Clinical Investigation Plan.

Including:

- CMS assessment;
- NRS assessment;
- ASES assessment.
- SST assessment;
- shoulder ROM assessment;
- assessment of painkiller drug consumption used in case of pain onset

through clinical diary;

- evaluation of any Adverse Events.

T12/FU(±7days):

At 12 months from day 0, i.e at the end of the Clinical Investigation, all the End Points set out in the Investigation Plan will be re-assessed.

Including:

- CMS assessment;
- NRS assessment;
- ASES assessment.
- SST assessment;
- shoulder ROM evaluation;
- MRI assessment;
- painkiller drug consumption assessment used in case of pain onset

through clinical diary;

- evaluation of any Adverse Events;

Diagnosis, evaluation of inflammatory and degenerative signs at MRI investigation of the shoulder with rotator cuff syndrome will be performed by the Principal Investigator.

The CMS, ASES, SST rating scales will be administered to the subject by the Co-Investigator. Recording of the clinical diary data regarding painkiller medication intake will be performed by the Co-Investigator.

The occurrence of Adverse Events will be assessed at each visit. All Adverse Events (AEs), Serious Adverse Events (SAEs) and Suspected Serious and Unexpected Adverse Reactions (SUSARs) occurring between the date of signing the Informed Consent and the end of the Clinical Investigation will be recorded and reported.

All data collected will have to be entered by the Data Manager in the Electronic Data Collection Form (e-CRF) provided by Guna S.p.a. The Principal Investigator and the Data Manager identified by him will be responsible for the correct entry of the collected data in the e-CRF.

In particular, it is planned to obtain a data collection that is schematically described in the following table (Tab. 1), which shows the entries to be made at each visit:

EXPERIMENTAL PROCEDURES	VISIT T0 Enrollment	VISIT T2weeks ± 2days	VISIT T4weeks ± 2days	VISIT T3 months ± 7days	VISIT T6/FU ± 7days	VISIT T12/FU ± 7days
Diagnosi clinica RCS	**X**					
Valutazione criteri di selezione	**X**					
Signing Informat consent	**X**					
Signing of privacy agreement	**X**					
Socio-demographic data collection	**X**					
Anamnestic collection	**X**					
NRS Assessment	**X**	**X**	**X**	**X**	**X**	**X**
CMS Assessment	**X**			**X**	**X**	**X**
ASES Assessment	**X**			**X**	**X**	**X**
SST Assessment	**X**			**X**	**X**	**X**
Shoulder ROM assessment	**X**			**X**	**X**	**X**
MR Assesment	**X**					**X**
Infiltrative Treatment	**X**	**X**	**X**			
Evaluation of clinical diary analgesic consumption.	**X**	**X**	**X**	**X**	**X**	**X**
Evaluation of clinical diary concomitant treatment for ongoing co-morbidities	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Event Evaluation (AE/SAE)	**X**	**X**	**X**	**X**	**X**	**X**

Tab.1 Data collection during the clinical Investigation

4.10 Material required for conducting the clinical investigation

The medical device necessary for conducting the investigation is MD-Shoulder *Collagen Medical Device* (GUNA, Milan-Italy) in 2 ml vials.

This material will be sent by Guna S.p.a. to the Pharmacy of the Experimental Centre with temperature-controlled shipment (range 15°-25°C) and in a quantity suitable for conducting the Clinical Investigation.

The medical devices will have to be stored by the Experimental Centre pharmacy and subsequently by the investigators within the same temperature range.

4.11 Study group

Only one experimental group is included in the investigation plan, which will be treated with 2 ml volume ultrasound-guided infiltrations of MD-Shoulder *Collagen Medical Device* (GUNA, Milan-Italy).

Composition per 2 ml: collagen 100 micrograms.

Excipients: Iris, NaCl, Water for injection. Subjects will be treated with no. 1 ultrasound infiltration at the time of enrolment, 2 weeks after enrolment and 4 weeks after enrolment.

4.12 Infiltration technique

Intra-articular infiltration will be performed with 5cc syringes and 22-gauge needles.

MD-Shoulder *Collagen Medical Device* will be infiltrated inside the scapulo-humeral joint under conditions of complete asepsis.

4.13.1 Effectiveness Criteria

4.13.2 Primary End Point

The primary End Point will consist of the evaluation, by means of the Constant-Murley Functional Scale (CMS), of the effectiveness, in terms of performance, of MD-Shoulder *Collagen Medical Device* in the recovery of joint function and reduction of associated pain at time months 3, i.e. 3 months after the first infiltration, compared to baseline (day 0). An increase of at least 15 points on the CMS scale is considered clinically significant.

4.13.3 Secondary End Points

The Secondary Endpoints will consist of evaluating the performance of MD-Shoulder *Collagen Medical Device* through:

- CMS at months 3, 6 and months 12 compared to day 0.
- NRS at week 2, week 4, months 3, months 6, months 12 compared to day 0
- ASES, SST and ROM at months 3, months 6, months 12 compared to day 0
- cuff integrity at months 12 compared to day 0 by performing MRI of the treated shoulder
- analgesic consumption at various phases of the study.
- evaluation of Adverse Events.

4.14 Data collection

All data resulting from the Clinical Investigation will be entered, within seven days of their collection, into the electronic Data Collection Form (e-CRF) "Pheedit Dedagroup" provided by the Sponsor. Radiological data will be collected and stored digitally on the PACS system. Data entry procedures will be performed by the Data Manager.

4.15 Early abandonment of the Clinical Study

I Subjects may leave the Clinical study for the following reasons:

a. at their own request (even without justification);

b. at the investigator's discretion.

c. if they experience an Adverse Event.

The reason for abandonment will be stated in the e-CRF.

5 STATISTICS

5.1 Sample size

This is a one-sample study. We assume that at baseline the expected mean value of the Constant-Murley score is 65.0 and that given the eligibility criteria this value is between 50 and 80, we can therefore estimate the mean value to be 65.0 ± 7.5.

It is also expected, that at the end of the treatment i.e. at months 3, using the alternative hypothesis Ha: $\Delta = 13$, compared to the null hypothesis H0: $\Delta = 0$, estimating that the standard deviation of the differences is sdiff ≤ 20. With these assumptions a sample of 24 patients has a power of 86.2% in discriminating a difference of 13 with a standard deviation of the differences of 20, if a Student's t-test for paired data is used. If the data were not Gaussian distributed, instead of using the nonparametric equivalent (Wilcoxon test, where the power would still be at least 82,8%), we would prefer - if possible - to use a non-linear transformation of the data.

5.2 Statistical analysis plan

5.2.1 Descriptive statistics

All data collected will be validated and subjected to descriptive case analysis.
Categorical, nominal and ordinal variables will be summarised by relative and absolute frequency tables. Continuous variables will be described by mean (and 95% CI), median (and 95% CI), range, standard deviation and coefficient of variation.

5.2.2 Primary Endpoint

The primary endpoint will be assessed by Student's t-test for paired data as already established in the section on sample size.

5.2.3 Secondary End Points

Secondary End Points will consist of evaluating the efficacy, in terms of performance, of MD-Shoulder *Collagen Medical Device* through:

- CMS at months 3, 6 and months 12 compared to day 0, using ANOVA with repeated measures within patient, or Friedman's test.
- NRS at week 2, week 4, months 3, months 6, months 12 compared to day 0using ANOVA with repeated measures within patient, or Friedman's test.
- ASES and SST at day 0, months 3, months 6 and months 12 using ANOVA with repeated measures within patient, or Friedman's test.

- cuff integrity at day 0 and months 12 by performing MRI of the treated shoulder using Clopper-Pearson binomial test.
- analgesic consumption in the various phases of the study, understood as dosage units/month and evaluated as mean, CI 95% of mean, median, CI 95% of median, SD and range.
- adverse events by records of the various AEs, SAEs, SUSARs according to § 6.4.

6 ETHICAL REQUIREMENTS

6.1 Ethical Authorisation

The Clinical Investigation Plan will be submitted to the relevant Ethics Committee for approval.

6.2 Amendments to the Clinical Investigation Plan

Any amendments to this Investigation Plan will be submitted by the Sponsor, in the form of an amendment, to the relevant Ethics Committee for approval.

6.3 Information to the Subject

The purposes and modalities of the Investigation will be explained to each subject by means of an information document (Informed Consent), containing what is verbally stated by the clinician. The subject must date and sign the consent document.
A copy of the document will be given to the subject while the original will be kept by the investigator.

6.4 Adverse Events

An Adverse Event is defined as any harmful clinical event that will occur during the course of the clinical investigation in one of the subjects comprising the study population who has undergone one of the treatments in the investigation plan.
Adverse events will be classified into serious (SAE) non-serious (AE) and Suspected Serious and Unexpected Adverse Reactions (SUSAR).

An Adverse Event is defined as serious if (ICH-GCP DM 15/07/1997):

- it causes the death of the subject involved in the investigation
- places the subject's life in danger
- is such as to require hospitalization
- is such as to require prolonged hospitalization
- is such as to cause permanent or temporary disability
- leads to a congenital anomaly or birth defect

In all other cases, the Adverse Event will be non-serious and will be classified as:
- *mild* does not interfere with normal activities of daily living and resolves spontaneously.

- *moderate*, interferes with activities of daily living but resolves spontaneously;
- *severe*, prevents daily life activities and does not resolve spontaneously.

All personnel who come in contact with study subjects must report Adverse Events reported by subjects to the Investigator, who has a duty to collect all possible data about them.

- Adverse events (AEs) will be reported within 48 h by the Principal Investigator to the Clinical Research Unit of Guna S.p.a, through telephone, email, appropriate form and simultaneously through e-CRF.
- Serious Adverse Events (SAEs) and Suspected Serious and Unexpected Adverse Reactions (SUSARs) will have to be reported to the Sponsor immediately (within 24 h maximum) through telephone, email, appropriate form and simultaneously through e-CRF by the Principal Investigator and communicated to the Ethics Committee and the Ministry of Health.

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The investigator should ensure that procedures are in place to ensure that the event is resolved.
In the case of nonserious Adverse Events (AEs), it is necessary to keep in mind that they can still give rise to serious events, which is why each Adverse Event must be monitored.
Adverse Events that have not yet resolved at the end of the study will be followed up by the Investigator; each subject who has experienced an Adverse Event will be contacted at least once a month after the conclusion of the study for as many months as deemed appropriate.

5.4. Privacy Protection

The identities of data subjects will be known only to the Investigators and the Clinical Monitor in charge of monitoring the investigation. Reference will be made to Regulation (EU) 2017/745.

Full respect for the anonymity of the subjects participating in the Clinical study will be ensured. Data collection, data processing, any scientific publications or congress presentations of the results of the Clinical Investigation will be conducted in accordance with the current Privacy Law - Regulation (EU) 2017/745.

6.5 Access to data

In compliance with the regulations in force concerning Clinical Investigations on medical devices, the Institute and the investigators will allow monitoring of the study according to the monitoring plan drawn up by the Sponsor. In addition, they will allow the Competent Authorities direct access to the study documentation being audited.

6.6 Data ownership

All data collected will belong to Guna S.p.a. Milan, Italy, Sponsor of the Clinical study.
Further information on data ownership can be found in the Economic Agreement document.

6.7 Data processing and publication

The results of this study will be summarised and presented in a final report that will aim to draw reliable conclusions regarding the clinical efficacy of the infiltrative treatment of rotator cuff syndrome by means of an infiltrative cycle with MD-Shoulder *Collagen Medical Device* injectable. The scientific article will then be edited and sent to a peer reviewed journal in the field for publication in order to disseminate the results obtained to the scientific community.

6.8 Funding

This research is financed by GUNA S.p.a.
Please refer to the Economic Agreement for further information.

6.9 Code of Ethics

Reference is made to the Declaration of Helsinki (Fortaleza 64th 2013) and the principles of Good Clinical Practice (GCP) are to be followed (D.leg. 24 June 2003 - n.211 in G.U. n.184 of 09/08/2003).

6.10 Subject Insurance

Insurance cover will be provided by GUNA S.p.a. for the entire duration of the clinical investigation project for all subjects enrolled.

5. PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The Investigators reserve the right to discontinue the investigation at any time for reasonable medical and/or administrative reasons. Reasons for discontinuation will be documented; the Ethics Committee and the Ministry of Health will be informed of the decision.

7 GLOSSARY

Medical device: Any instrument, apparatus, implant, substance or other product, whether used alone or in combination, including computer software used for proper functioning, and intended by the manufacturer for use in man for the purpose of diagnosis prevention, control, therapy or mitigation of a disease; diagnosis, control, therapy, mitigation or compensation for an injury or handicap of study, replacement or modification of anatomy or a physiological process; of intervention in conception, which product does not exert its principal action, in or on the human body, for which it is intended, by pharmacological or immunological means, nor by metabolic process but whose function may be assisted by such means.

8 ATTACHMENTS TO THE INVESTIGATIONAL STUDY PLAN

A. Informed Consent (disclosure and consent)
B. Consent to the processing of personal data (information and consent)
C. Clinical diary
D. Constant-Murley Score (CMS)
E. Numeric Rating Scale (NRS) - American Shoulder and Elbow Surgeons (ASES) – Simply Shoulder Test SST
F. Range Of Motion (ROM) of shoulder

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