Multicenter, Controlled and Randomized Clinical Trial to Evaluate the Combined Use of a Medical Device and a Food Supplement in the Control of Urinary pH in Patients with an Implanted Double Pigtail Stent

Protocol code: DEV-LCD-02-17

CLINICAL TRIAL PROTOCOL

(Version 1.2)

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Collaborating researchers:

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CONFIDENTIAL

SIGNATURE PAGE OF THE PROTOCOL

PROTOCOL: DEV-LCD-02-17

I have read this protocol and agree to conduct this clinical trial in accordance with all the stipulations of the protocol, the current legislation and the Declaration of Helsinki.

EMERGENCY NUMBERS

In case of urgency, contact quickly by telephone with the responsible doctor and / or with the person responsible for the monitoring of the trial.

PRINCIPAL INVESTIGATOR

TRIAL MONITORING			
RESPONSIBLE OF TRIAL MONITORING	OFFICE TELEPHONE NUMBER	TELEPHONE NUMBER OUT OF WORK TIME	FAX NUMBER

1 SUMMARY

1.1 Title

Multicenter, Controlled and Randomized Trial to Evaluate the Combined Use of a Medical Device and a Food Supplement in the Control of Urinary pH of Patients with an Implanted Double J Stent.

1.2 Protocol code

Promoter Code: DEV-LCD-02-17

1.3 Promoter

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1.8 Ethical Research Committees (CEI)

All study materials have been reviewed and approved by:

- CEIC of the Hospital Universitari de Bellvitge (CEIm)

1.9 Description of the intervention between the arms of the trial (experimental and control):

EXPERIMENTAL ARM

• Food supplement study (II): Lit-Control® pH Down

o Pharmaceutical form: capsules
o Route of administration: oral
o Dosage: 3 capsules / day.

• Study medical product: Lit-Control® pH Meter

o Classification: in vitro diagnostic medical device.
o Use: assessment of urinary pH.
o Valuation method: by field effect transistors.
o Periodicity of use: 1 time a day in the morning (first urine).

CONTROL ARM

• Placebo:

o Pharmaceutical form: capsules
o Route of administration: oral
o Dosage: 3 capsules / day.

• Study medical product: Lit-Control® pH Meter

o Classification: in vitro diagnostic medical device.
o Use: assessment of urinary pH.
o Valuation method: by field effect transistors.

o Periodicity of use: 1 time a day in the morning (first urine).

1.10 Phase of the clinical trial

Post-marketing.

1.11 Objective

Principal:

- To evaluate the efficacy of the food supplement Lit-control® pH Down in the prevention of double J stent calcification.

Secondary:

- Evaluate the efficiency of the Lit-control® pH Meter device and the Lit-control® pH Down food supplement in the pH control.

- Determine the safety of the food supplement Lit-control® pH Down.

- Evaluate compliance / adherence with the measures for the determination and control of pH recommended by the doctor.

- Know the cost-effective profile of the intervention (from the moment of placing the double J stent to its withdrawal).

1.12. Study design

Multicenter, prospective, randomized, double-blind, placebo-controlled study.

1.13. Disease under study

Process of calcification of the double permanent stent J.

1.14. Type of study

Clinical trial with sanitary product.

1.15 Study population

Adults who come to the urology / nephrology clinic who have recently had a double J stent or who have scheduled their placement and who are able to take charge of the urinary pH control at home.

1.16. Monitoring

Clever Instruments S.L. will be responsible for the logistics and monitoring of the study. A monitoring visit is planned to start and close the study by center. Real-time remote monitoring of the data record will be done throughout the study.

1.17. Treatment duration

Health product under study: 2 months (1 use / measurement per day).
Food supplement object of study: 2 months (3 capsules per day).

Placebo: 2 months (3 capsules per day).

1.18. Expected duration of the clinical trial

The expected duration for the recruitment of patients will be 3 months with a follow-up period until the stent is extracted, which is expected to be a maximum of 2 months

Contenido

2. INTRODUCTION AND JUSTIFICATION OF THE STUDY

Since the introduction of double ureteral stent J by Finney in 1978, its use has taken an important position in the management of obstructive uropathy (urolithiasis, stenosis and ureteral injuries, retroperitoneal fibrosis), in the postoperative period of ureteropyelic stenosis and transplantation renal.2 The most severe complication associated with the use of the double J stent is calcification and the potential impossibility of removing the ureteral stent.3,4 The incrustation process that results in the calcification (partial or total) of the stent was described in 1995 by Getliffe as the "embedding cycle" .5, 6 This cycle begins with colonization of the stent or urinary tract infection (UTI) by urea-releasing microorganisms, which contribute to an alkalinization of urine and a decrease in solubility of minerals in urine, facilitating the possibility of incrustation and subsequent calcification.5 This process occurs faster in some patients is that in others, suggesting that there are patients more likely to have this complication.7

Several studies have shown the importance of urinary pH control (pHv) to determine the frequency of stent incrustation, 8-10 this measure being a variable to be taken into account in the management of patients with indwelling stent. However, the level of pHv is influenced by multiple factors, so its routine control is difficult to interpret.11 Choong et al. (1999) described the nucleation pH (pHn): the pH where the scale starts to form.12 In his study he observed that the pH of the patients who developed a stent blockage and those who were not very similar (7.46 and 7.38 respectively), but observed that the pHv of the patients who did not have incrustations was much lower and therefore had a much wider safety margin.12

As already mentioned, pHv is influenced by various factors, but it is especially sensitive to diet.10 For this reason, hygienodiethetic interventions (exercise, diet, fluid intake, etc.) are one of the preventive measures of incrustation of the stent of great utility, although its effectiveness is subject to patient adherence.

Lit-control®pH Down is a dietary supplement with an acidifying effect on urine, which helps to prevent complications arising from the alkalinization of urine. It contains L-methionine, phytin (calcium-magnesium phytate salt), zinc and vitamin A. The two active components in acidification of pHv are L-methionine and fintine, while zinc and vitamin A increase the action of the phytin Specifically, zinc favors the affinity of its affinity for calcium phosphate and vitamin A prevents its degradation by alkaline phosphatase.

L-methionine is an essential amino acid that plays an important role in metabolic processes. It is normally acquired through food and absorbed in the small intestine to be metabolized in the liver via cysteine to sulphate and protons (ANNEX 8). Consequently, its administration produces a significant reduction of urinary pH.

According to the European Association of Urology (UAE), urinary acidification with L-methionine up to pH 5.8 - 6.2 is recommended as a therapeutic measure for calculations of struvite, calcium phosphate and ammonium urate at doses of 600- 1500 mg / day13. This recommendation is based on the results observed in Jarrar et al 199614, where an acidification of the pH of the urine of the patients was observed from 7.5 to 5.5 after the administration of 1500-3000 mg / day (3-6 capsules). of 500mg / day). Also in the study of Hesse 1999 a significant reduction in urinary pH was observed up to pH = 6.0 after the administration of a single dose of 1500 mg of L-methionine, maintaining this effect for 24h15. In addition, a significant reduction was observed versus the control group in terms of the relative supersaturation for estuvite and

brushite in the urine of 24h15. In another more recent study, Siener et al. studied the circadian course of urinary pH after the administration of 1500 mg of L-methionine. They observed a strong decrease in urinary pH up to 2h after the administration of the amino acid that remained at significantly low levels for 8h, resulting in a pH level for 24h between 5.98 and 6.3216. Therefore, in order to guarantee therapeutic doses of L-Methionine (1500mg / day), the Lit-control®pH Down regimen to follow would be equivalent to 3 capsules per day (500 mg / capsule).

On the other hand, the device Lit-control® pH Meter is a medical device that allows patients to self-monitor their pHv daily in their own home, allowing a thorough control of the pH and the level of encrustation risk. The device has been validated for use in lithiasic patients17, with applicability in the treatment of other urological pathologies related to the acid-base balance of urine, calcifications of urinary stents, cystitis, urinary tract infections, painful bladder syndrome and bladder hyperactive

The aim of this study is to evaluate the efficacy of the food supplement Lit-control®pH Down in the prevention of the double J stent incrustation and in the urinary pH control together with the use of the Lit-control® pH Meter device.

3. OBJECTIVES OF THE STUDY

3.1 Main objective

- To evaluate the efficacy of the Lit-control®pH Down food supplement in the prevention of double J stent calcification.

3.2 Secondary objectives

- Evaluate the efficiency of the Lit-control® pH Meter device and the Lit-control®pH Down food supplement in the pH control.

- Determine the safety of the food supplement Lit-control®pH Down.

- Evaluate compliance / adherence with the measures for the determination and control of pH recommended by the doctor.

- Know the cost-effective profile of the intervention (from the moment of placing the double J stent to its withdrawal).

4. INFORMATION SOURCE

The information will be obtained from the data collected during the clinical visit, as well as from the data recorded by the patients themselves and the self-administered scales of the Questionnaires and Data Collection Notebooks that the researchers will deliver / administer. The researcher will be responsible for the study data being registered in the electronic CRD (eCRD).

5. SCOPE WHERE THE STUDY IS PERFORMED

National urology / nephrology consultations.

6. STUDY DESIGN

6.1 Type of study

Clinical trial with medical device (Lit-control®pH Meter device). Multicenter, prospective, randomized, double-blind, placebo-controlled study in adult patients who come to the urology / nephrology clinic who have recently had a double J stent or have their placement programmed and who are able to take charge of the urinary pH control at home.

They will be randomized into two groups (experimental group (Lit-control®pH Meter + food supplement Lit-control®pH Down) and control group (Lit-control®pH Meter + Placebo)). The ratio will be 1: 1 between the experimental group and the control.

In accordance with the current Royal Decree 1090/2015, of December 4, which regulates clinical trials with medicines, the Research Ethics Committees with medicines and the Spanish Registry of Clinical Studies, 18 a new type is contemplated a "low level of intervention" test in which less rigorous standards are adopted in aspects such as monitoring, the content of the master file or traceability, without impairing the safety of the individuals who participate in them. This concept was introduced by Regulation (EU) No. 536/2014 of the European Parliament and of the Council of April 16, 2014,19 which quotes verbatim:

"The risk to the safety of the test subjects comes mainly from two sources, the investigational drug and the intervention, but many clinical trials pose an additional risk to the safety of the subjects that is minimal compared to that of clinical practice. habitual. This is so, specifically, when the investigational medicinal product already has marketing authorization, which means that its quality, safety and efficacy were already evaluated during the authorization procedure or, if that medication is not used in accordance with the conditions of the marketing authorization, when its use is based on evidence and is supported by documented scientific data on the safety and efficacy of that medicine, and the intervention only involves a very limited additional risk for the test subject, compared with that of the practice usual clinic. "

In the same regulation, a "low-level intervention clinical trial" is defined:

a) investigational drugs, excluding placebos, are authorized;

b) according to the protocol of the clinical trial:

i. the investigational drugs are used in accordance with the terms of the marketing authorization, or

ii. the use of investigational medicinal products is based on evidence and is supported by published scientific data on the safety and efficacy of such investigational medicinal products in one of the Member States involved, and

c) complementary diagnostic or follow-up procedures involve a risk or additional burden for the safety of the subjects that is minimal compared to that of usual clinical practice in any of the Member States involved.

In the present study, the condition of "low level of intervention" is requested since both products are phymeter (Lit-control® pH Meter) and food supplement (Lit-control®pH Down), marketed and represent a minimum risk for safety of the patient. The Lit-control® pH Meter medical device is a proven and validated safety and efficacy device for the determination of urinary pH, the use of which does not imply any risk for the user. On the other hand, hygienic-dietetic measures are a recognized and recommended intervention to decrease urinary pH, but

given the difficulty of introducing drastic changes in the diet effectively, this essay aims to study the effect of dietary supplementation, which implies a minimum intervention level and a practically zero risk for the patient.

The recommended dose of the Lit-control®pH Down food supplement is 2 capsules daily, but taking into account the recommended daily consumption according to the European Food Safety Authority (EFSA) of the components of Lit-control®pH Down, it could be extended to a maximum dose of 6 capsules daily, the "limiting factor" being the daily intake of zinc. A total of 3 capsules would correspond to 4.3 mg / day of elemental zinc, this being an amount within (below) the recommended daily requirements 7.3 mg / day and 5.5 mg / day for men and women respectively and it would be far from the NOAEL established at 50mg / day by the same ESFA from the available studies20,21. Similarly, the limit for the prolonged zinc supply of> 25 mg established by the ESFA in which it must be specified on the label of the product that can produce anemia is also a value well above the daily intake proposed for the patients of the study22.

With the data mentioned above and based on the available evidence, the appropriate dose for the patient profile of the trial has been estimated at 3 capsules daily to be able to reach adequate doses of L-Methionine (the component responsible for acidification of urine) compatible with the therapeutic dose of 1500 mg / day observed in previous studies. In addition, this is the recommended dose according to the EAU guidelines on diagnosis and conservative management of urolithiasis13 to acidify urine. In the section of the justification of this protocol the discussion on this point is extended.

6.2 Study population

Adults who come to the urology / nephrology clinic who have recently had a double J stent or who have scheduled their placement and who are able to take charge of the urinary pH control at home.

6.2.1 Inclusion criteria

• Age ≥18 years.

• Patients who have recently had a double J stent (time less than a week) or who have scheduled their placement and are recommended to control the pH to avoid scaling / calcification.

• Patients who agree to participate in the study and provide their informed consent.

6.2.2 Exclusion criteria

• Patients with basic pathologies that, according to the researcher's criteria, are not susceptible to the recommendation of the food supplement object of study.

• Patients who have scheduled the extraction of the double J stent before 3 weeks from the baseline / inclusion visit.

• Uric and cystinuric patients that require pH control different from that established in the study protocol.

6.2.3 Discontinuation criteria

• Withdrawal of informed consent.

• Violation of the protocol.

• Patients with early withdrawal of the double J stent (time less than 3 weeks after the baseline visit).

• Use of other food supplements not specified in this protocol that could interfere with the evaluation of the efficacy of the supplement under study.

• Serious Adverse Event (AAG).

• Abandonment of the study.

6.3 Observation period

6.3.1 Inclusion period

The urologist / nephrologist will recruit patients as they come to the consultation and meet the inclusion and exclusion criteria, according to the consecutive sampling technique. The assignment of the study treatment will be carried out randomly, according to the previously established code that will be assigned to each patient as they are included in the study.

The expected duration for the recruitment of patients will be 3 months with a follow-up period until the stent is extracted, which is expected to be a maximum of 2 months. The recruitment of the participating centers will be competitive.

6.3.2 Follow-up period

The follow-up will be 3 weeks up to a maximum of approximately 2 months, depending on the time from the inclusion visit (V0) to the extraction of the stent (Vf). During this period, the patient will self-monitor their urinary pH level at home and register the respective data with the domiciliary CRD. The patient will be offered the possibility of registering the home self-management data directly to an online CRD through a personalized link that the researcher will provide during the inclusion visit and that will be generated through a computer program. If you only register it on paper, you must deliver it to the researcher at the next visit.

6.3.3 Baseline Visit - V0 (inclusion)

The researcher will consecutively include the patients as they come to their consultation. The investigator will inform the patient about the study and will provide the information sheet. In case the patient agrees to participate in the study, they must sign the informed Consent Form that the researcher will also provide. Subsequently, the researcher will ensure that the patient meets all the inclusion / exclusion criteria and proceed to confirm their inclusion in the study. If the patient is eligible but does not give informed consent and / or does not meet any of the inclusion / exclusion criteria, then the investigator will add a new case to the list of eligible patients without recording any other information related to the patient.

Sociodemographic data and medical and family history of interest will be recorded, as well as the date and reason for stent placement. The data will be recorded necessary to classify patients according to the "Blockage risk factor" 23. In addition, a urine test of 2 hours fasting will be requested.

At the end of the visit, the patient will be given the treatment assigned by randomization and the link to the electronic domicile CRD and on paper. The patient will be reminded that at the next visit they should return (empty or not) the blisters of the treatment administered.

NOTE: For reasons derived from the logistics and the tests to be performed with the stent, researchers should try to enter the data in the online CRD in real time (or within a 24 hour timeframe) both at the time of placement of the stent as of extraction. This will allow a follow-

up and an appropriate time of logistical management that guarantees that the stents arrive in optimal conditions for their study to the specialized center of Palma de Mallorca.

6.3.4 Visit Final Control - Vf (stent removal)

The time of the final visit will not be determined by protocol but according to the moment in which, by usual clinical practice, the double j stent is extracted in a programmed manner (which should be between 3 and 8 weeks after the baseline visit). During this visit, the data regarding the symptoms perceived by the patient during the time with the stent will be recorded, data relative to the received treatment (adherence, presence of adverse effects, date of beginning and end of the pH control, complications derived from the stent and data on stent removal (date, complications, presence / degree of calcification, etc.) and this will be sent (after conditioning) * to be analyzed by an expert to determine the presence of any of the different stages of calcification (presence of bacterial biofilm, incrustations and / or calcifications.) During this visit, the patient will deliver his / her home diary with the pH control data and annotated supplement record (as long as it has not already been registered directly with the home eCRD) and will also transfer the product excess (food supplement blisters) and, if possible, also empty blisters.

On the other hand, pharmacoeconomic data will also be recorded in order to determine the cost-effective profile of the intervention.

* The conditioning of the stent for storage and subsequent delivery to the specialist who is going to carry out his study is described in the Investigator's Manual.

6.4 Description of the intervention

The patients of the experimental group will receive the food supplement Lit-control®pH Down to help maintain the urinary pH at the levels considered as preventive for stent calcification (pH <6.2), with the indicated guideline of 3 capsules per day . On the contrary, the control group will receive a placebo product with similar organoleptic characteristics with the same dosage. Both groups will use the Lit-Control® pH Meter device for urinary pH self-monitoring as well as receiving the same indications for stent care.

The intervention group will be assigned to each patient according to the assigned code in order of inclusion to the study and that will serve for the randomization of the patients.

6.5 Randomization

Patients will be randomized into two groups according to whether they receive the dietary supplement Lit-control®pH Down or placebo. The random assignment of patients will be implicit in the code that will be assigned consecutively in each center. The code lists for the centers will be previously prepared through an ad-hoc program. The ratio between placebo and Lit-Control® pH Down will be 1: 1. Being a competitive inclusion, the randomization numbers will be distributed in blocks of 5 for each center, with an average of three deliveries per center.

6.6 Concomitant treatments

The existence of concomitant treatments will be recorded. Only those treatments likely to influence the results of the trial will be grounds for withdrawal from the study (see section 6.2.4).

6.7 Compliance with the intervention

Compliance with the indicated intervention will be verified with the data recorded in the Patient's Home Journal, with direct questions in the control visits and the empty blisters returned by the patients in the Vf.

6.8 Predetermination of the sample size

For the calculation of the sample size, the non-parametric Mann-Whitney U test was used for independent groups in order to observe, on a 4-point stent calcification scale (0-3), a difference equivalent to a size Effect of 0.6.

Thus, considering a statistical power of 80% and a non-normal distribution, a sample size of 94 patients is obtained. In anticipation of a 10% loss, the sample is extended to 105 patients.

7 VARIABLES AND MEASURING INSTRUMENTS

7.1 Main valuation variables

- Score on the scale of incrustation (main variable of effectiveness):

or 0 (Without inlay).

or 1 (Sporadic calcifications less than 1-2 mm2).

or 2 (Calcifications of wide areas greater than 1-2 mm2).

or 3 (Complete block).

- Urinary pH level and control of it below 6.2 (urine 2h fasting and home self-control with Lit-control®pH Meter).

- Reason for stent placement (approximately 90% is expected to be urolithiasis).

- Obstruction risk factor23.

- Stent analysis / observation (presence of biofilm, degree of incrustation).

- Double J stent study:

o Scanning electron microscopy + micro-analysis by dispersive energy of RX: type and size of the crystals formed.

or ICP-AES spectroscopy (degree of global calcification of each end: Ca, Mg and P).

- Presence (Yes / No) and Degree of calcification (I-V) (Annex 7) 24.

7.2 Secondary valuation variables

- Sociodemographic and anthropometric variables (sex, age, weight, height, BMI, marital status, work situation, toxic habits).

- Family history of obstructive uropathies.

- Personal clinical history of interest (previous nephritic colic, kidney transplant, acute pathology of interest, chronic pathology (HBP, Chronic Kidney Disease, Diabetes and others).

- Anatomical alterations in the urinary system.

- Previous incidence of obstructive uropathy (urolithiasis, stenosis and ureteral injuries, retroperitoneal fibrosis).

- Previous need for stent (indwelling stent reason, date of stent placement and removal, type of stent and symptoms (if any) associated with it)

- Date of placement and removal of the double J stent (current) and Total time with double J stent until its withdrawal (days).

- Total pH control time (days).

- Urine analysis of 2 hours in basal fasting (volume of urine, pH, creatinine, uric acid).

- Urine culture (infection: yes / no).

- Complications observed due to placement or permanence of the stent and symptoms associated with indwelling stent.

- Image of the stent (scanner or X-ray).

- Adherence to treatment / recommendations of the doctor.

- Adverse events attributable to the treatment or study recommendations.

- Data on stent removal (date, complications, type of procedure and duration of extraction).

- Satisfaction of the researcher with preventive therapy.

- Patient satisfaction with preventive therapy.

- Pharmacoeconomic data (direct costs): stent placement intervention, consultation visits, emergency visits, hospitalizations, medication administered, intervention (cost and type) for stent removal and total direct cost of the patient during the study (estimated at from the data provided by the center).

7.3 Tools

- pH scale and cut points.

- Lit-Control® pH Meter device for measuring urinary pH (home self-monitoring).

- Scale of incrustation / blocking of the stent (0 / Without inlay - 3 / Complete block).

- Blockage risk factor (Clifford et al, 2000) 23 (in order to better characterize the sample studied) (See Annex 2).

7.4 End points

- Profile / Characteristics of the patient to whom a double J stent is placed.

- Comparison between groups of the results of the stent study (type and size of the crystals formed and degree of global calcification of each end).

- Success rate in pH control below 6.2 during the study.

- Percentage of stent extractions in the first attempt.

- Rate of complications in the extraction of the stent.

- Rate of adverse events attributable to treatment.

- Percentage of patients compliant (adherence> 80%) of the study interventions at 8 weeks (final visit).

- Degree of satisfaction of the researcher with the results of pH control.

- Degree of patient satisfaction with the use of the products under study.

- Cost-effectiveness of the intervention object of study according to the direct costs observed.

8 STATISTICAL ANALYSIS

All data will be analyzed using the statistical package SPSS-Windows.

8.1 Descriptive statistics

A descriptive statistic of all the variables collected in the CRD will be made.

The categorical variables will be presented in the form of lists of frequencies and proportions. For the quantitative variables (continuous or ordinal), indices of central tendency (mean, median, mode) and dispersion (standard deviation and maximum and minimum values) will also be presented.

8.2 Objectives of the study

In order to analyze the differences between continuous qualitative variables between the experimental group and the control, the T-Student test will be used for two independent samples, in case the condition of normality can be accepted.

variables in each of the groups. Otherwise, we will proceed with its non-parametric counterpart: U-Mann-Whitney.

In the case of the qualitative variables included in the CRD, the test to be used will be Chi-Square or through Fisher's exact test (when the percentage of expected values less than 5 exceeds 20%).

The possibility of carrying out additional analyzes, depending on the results, with the relevant statistical tests in each case is not ruled out.

9 ETHICAL CONSIDERATIONS

9.1 General considerations

This study should be developed in accordance with what is established in this protocol and with the standards of Good Clinical Practice (GCP), as described in:

• Harmonized Tripartite Rules of the ICH for Good Clinical Practice 1996. Directive 91/507 / EECC: Good Clinical Practice Standards for testing of medical products in the European Community.

• Declaration of Helsinki in its latest revised version (Fortaleza, 2013) (Annex-1)

The study will only begin after having obtained in writing the authorization of the Research Ethics Committee of the Univeristario de Bellvitge Hospital (Hospitalet de Llobregat, Barcelona) that acts as reference center (CEIm).

With the exception of those emergency situations, changes or deviations from the protocol will not be allowed without documented approval.

The CEIm must be informed of possible changes and will approve in writing any change or deviation that may increase the risks of the subject and / or adversely affect the rights of or the validity of the investigation. This stipulation does not apply to those changes that are made to reduce the inconvenience or avoid risks to the subjects and to the changes that affect the administrative aspects of the study (eg, change of monitor).

9.2 Evaluation of the benefit-risk of the investigation

In any case, the patient will receive a specific therapeutic alternative and according to the diagnosis established by the researcher, so the suitability of the study treatments will not increase the risk for patients.

If the investigator does not perceive a lack of efficacy of the treatment, adverse effect or complication, he / she will be able to discontinue the patient at any time. Similarly, the patient is free to leave the study at any time without affecting his medical care.

9.3 Information sheet and informed consent

The investigator is responsible for ensuring that the patient (and / or legally authorized representative) understands the risks and benefits of their participation in the study, answering any questions that may arise during the study, and sharing any timely new information that could influence the decision to continue their participation in the study.

The patient (or his legal representative) will be informed of the characteristics of the clinical trial, verbally and in writing, through the INFORMATION SHEET.

Finally, after being fully informed of the implications and restrictions of the protocol, having answered their questions and before starting the study, the patient will be asked to give an INFORMED CONSENT in writing. The patient information sheet model and the informed consent form are attached as an annex to this protocol. By signing and dating the informed consent form, the subject declares their voluntary participation and their intention to comply with the Study Protocol and the Investigator's Instructions and respond to issues that arise throughout the Study.

The subject will keep the information sheet throughout the study, with all the relevant study information, including the researcher's contact. The researcher must keep the informed consent in the study file.

9.4 Review of the Ethics Committee

This protocol will be approved by the Research Ethics Committee of the Hospital Universitario de Bellvitge (Hospitalet de Llobregat, Barcelona), which will act as a reference committee for the rest of the participating centers.

Any member of the Ethics Committee, who has a direct relationship with this study as an investigator or as a center staff, will abstain from voting to approve the protocol.

All changes to the protocol will be specified in the form of an amendment. The method of realization of the amendments will follow the standardized procedures according to RD 1090/2015, of December 4.

9.5 Confidentiality of the data

By signing the protocol, the researcher undertakes to keep all the information provided by the Promoter in strict confidentiality and that he will insist on the maintenance of the same by his team and the CEIm. The study documents provided by the Promoter (protocols, researcher's manual, CRDs and other materials) should be conveniently stored in the investigator's file, to ensure confidentiality. The researcher will in turn ensure that the researcher's file is kept in accordance with the conditions specified in Directive 2001/20 / EC.

The researcher will ensure the maintenance of the anonymity of the participating subjects. Both in the CRDs and in other EC documents, the subjects can not be identified by their names but by an identification code. The researcher will keep a record of the inclusion of subjects that shows the codes, names and contact information.

The information provided to the researcher by the Promoter may not be disclosed to third parties without the direct written authorization of the former, except to the extent necessary to obtain the informed consent that they wish to participate in this EC.

The information obtained will be considered strictly confidential based on Organic Law 15/1999, of December 13, on the Protection of Personal Data. (BOE No. 298, of 14-12-1999, pp. 43088-43099) and its development regulations. The collection of medical data will be done in accordance with Recommendation n. R (97) 5 of 13 February 1997, of the Committee of Ministers of the Council of Europe to the Member States on the Protection of Medical Data.

9.6 Records in CRD and reports

The researcher must ensure the accuracy, completeness and timeliness of the data communicated to the promoter in the CRD and in all requested reports. The data will be registered in an online CRD to which only the researcher will have access through a user and a personal and non-transferable password. All the data obtained will be stored in an electronic file of restricted access to the staff of each center and of which the principal investigator will be responsible.

Any change or correction to a CRD should be requested to the CRO in charge of monitoring, Clever Instruments S.L., contacting the person in charge of the data management designated by the promoter of the study. Changes must be documented and the researcher must keep records of changes and corrections.

Researchers or the institution must maintain the EC documents, as required by the applicable regulations. The investigator or the institution must take measures to prevent accidental or premature destruction of such documents.

Upon request of the monitor, auditor, CEIC or regulatory authority, the investigator / institution must have available all records related to the EC.

9.6.1 Monitoring Reports

The promoter or the CRO shall send written summaries of the status of the test to the CEIm annually, or more frequently, if so required by the CEIm.

The promoter or the CRO must provide punctual written reports to the CEIm and, when pertinent, to the institution about changes that significantly affect the development of the trial and / or increase the risk for the subjects. The investigator must supervise and sign these reports.

9.6.2 Security Reports

The promoter must be informed immediately of all serious adverse events, except those that are specified in the protocol or other document. It will be reported quickly, in writing, in detail and in the time periods specified by the promoter in the protocol. These follow-up reports must identify the subjects by means of the codes assigned in the CB and not by the names of the subjects, personal identification numbers and / or addresses.

9.6.3 Premature Termination or Suspension of the Protocol

If the study ends prematurely or is suspended for any reason, the investigator / institution should promptly inform the study subjects, providing appropriate therapy and follow-up. Further:

• If the researcher completes or suspends the study without prior agreement with the promoter, the researcher should inform the institution when appropriate, and the researcher / institution should promptly inform the promoter and the CEI, as well as send an explanation to the promoter and CEI Detailed written explanation of the termination or suspension.

• If the promoter completes or suspends the study, the investigator should promptly inform the institution when appropriate and the investigator / institution should promptly inform the CEI, sending a detailed written explanation of the termination or suspension

• If the CEI withdraws approval of the study, the investigator should inform the institution when appropriate and the investigator / institution should notify the promoter promptly and provide a detailed written explanation.

9.6.4 Investigator's Final Report

At the end of the study, the researcher, when appropriate, should inform the institution. The researcher / institution must provide the CEI with a summary of the results of the study.

9.7 Monitoring

It is established that the development of the study will be followed at regular intervals. The monitoring will be carried out by the monitor (s) designated by the Promoter. Regular contacts will be established between the Monitor / s and the Investigator.

It will be the responsibility of the Monitor to verify compliance with the protocol and the integrity, consistency and reliability of the data entered in the CRDs. For this, the monitor must be able to access the participant's medical history and other documents. The researcher or his collaborators agree to cooperate with the monitor to ensure that the detection of any problem in the course of monitoring is resolved.

Extraordinary audits can be carried out to guarantee the validity of the study data and compliance with the regulations in force.

9.8 Budget of the study

The economic aspects of the study are detailed in the corresponding annex and that supposes a separate document.

9.9 Insurance

As this is a low-level intervention study, it will not be necessary to take out insurance, as long as the individual or collective professional civil liability insurance (or equivalent financial guarantee) of the health center where the clinical trial is carried out covers the damages and damages that participation in the study may cause to patients. Such procedure will be done in accordance with the legislation of RD 1090/2015 (Annex 6: Certificate of the representative of the center / organization for clinical trials of low level of intervention)

10. PREPARATION AND CONSERVATION OF THE PRODUCT

10.1 Conditioning

The product under study (Lit-control®pH Meter and Lit-control®pH Down) must be stored by the researcher in a dry and safe place. Sufficient product will be assigned for the sample calculated in the sample calculation taking into account the initial / theoretical distribution of patients per center and that in the experimental group should be delivered during the baseline product visit for the duration of the entire study.

10.2 Labeling EC sample, products or treatments

Being a double-blinded placebo study, the researcher will deliver a box with no other distinctive than the patient and clinical trial code that will contain the Lit-control®pH Meter device and the Lit-control food supplement. ®pH Down or placebo depending on the arm where the patient is randomized. In addition, Lit-control®pH Down packaging boxes and the placebo will be designed and labeled for the trial to ensure double masking of the study.

10.3 Preservation, dispensation and return

The products provided for the EC should be stored at room temperature in a restricted access area free of extreme environmental conditions. It must be an area that can be closed with limited access to the researcher.

At the reception, an inventory of the shipment must be made; the document must be signed by the researcher or authorized person and a copy will be sent to the Monitor and another to the Investigator's Archive.

The researcher will be responsible for the return of the products, should document any discrepancies in the records of formula stocks.

11 ADVERSE EVENTS

The Adverse Events (AA) produced during the study will be evaluated. An AA is defined as any harmful event in a patient after randomization and during the performance of a study, even if it is considered not to be related to the treatment of the study. In this CE, the AAs in the CRD will be collected and recorded, as long as they are serious (if they cause clinical signs or symptoms and are considered clinically significant).

Diseases or medical conditions that were present before administering the product under study, will only be considered as AA if there is a worsening after the start of the study intervention (any procedure specified in the protocol).

To the extent possible, AAs will be described based on:

• Duration (start and end dates).

- Degree of severity (mild, moderate, severe).
- Relationship with the study medication (suspected / not suspected).
- Action (s) taken to correct it.

11.1 Types

Any unfavorable and unintended sign (abnormal and clinically significant analytical result), associated or not with the use of drugs, will be assessed as an adverse event.

11.2 Serious Adverse Events

Information on Serious Adverse Events (AAG) and Unexpected Serious Adverse Reactions (RAGI) with suspected causal relationship with the treatments under study, will be collected and recorded in the notification form of Serious Adverse Events (RD223 / 2004). Such serious adverse events must also be notified to the AEMPS, which will be done from the ESIC and for this the investigator must notify it within 24 hours of its knowledge. Only serious, unexpected AAs related to the treatments under study will be reported to the AEMPS.

AAG or RAGI is considered any adverse event or adverse reaction at any dose:

- Produce death of patients,
- Threatens the subject's life,
- Make necessary the hospitalization of the subject or the prolongation of it,
- Produces disability or permanent or significant disability, or
- Lead to an abnormality or congenital malformation.

The intensity of AA will be classified as mild, moderate or severe. The researcher will record the relationship of the study product with the AA according to the following causality terms:

- Related: the AA follows a reasonable time sequence from the moment of exposure to the product. It can not be explained by the clinical condition of the subject or by the procedures / conditions of the study. AA decreases after discontinuation of the study product and reappears once the study product is re-administered.

- Possibly related: the AA follows a reasonable temporal sequence from the moment of exposure to the product, but it may have been caused by the clinical condition of the subject or by the procedures / conditions of the study.

- Improbably related: the temporal association between the AA and the product of the study is such that it is unlikely that there is any reasonable relationship between them. The relationship is not likely due to other possible explanations.

- Not related: the AA, without a doubt, has been caused by the clinical condition of the subject or by the procedures / conditions of the EC. A reasonable explanation must be given, for example, that the product under investigation or an incompatible temporal relationship has not been consumed.

- Not evaluable: the report that indicates an adverse reaction can not be judged because the information that is counted is insufficient or contradictory, and no extra data can be added or the existing ones can be verified.

11.3 Action taken and resolution of AA

The researcher will record the action / s taken with the product and the effects of the event for each of the AAs, according to the following:

- Action taken in relation to the product.

- Resolution.

11.4 Follow up with AA

Patients can be withdrawn from the EC at any time. Patients withdrawn from the study due to an AA should be followed up by the investigator until the clinical outcome of the AA is determined.

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ANNEX 1: DECLARATION OF HELSINKI

DECLARATION OF HELSINKI OF THE WORLD MEDICAL ASSOCIATION

Ethical principles for medical research in humans

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

48th General Assembly Somerset West, South Africa, October 1996

52nd General Assembly, Edinburgh, Scotland, October 2000

Clarification Note of Paragraph 29, added by the General Assembly of the AMM,

Washington 2002

Clarification Note of Paragraph 30, added by the General Assembly of the AMM,

Tokyo 2004

59th General Assembly, Seoul, Korea, October 2008

64th General Assembly, Fortaleza, Brazil, October 2013.

Introduction

1. The World Medical Association (AMM) has promulgated the Declaration of Helsinki as a proposal of ethical principles for medical research in humans, including the investigation of identifiable human material and information.

The Declaration should be considered as a whole and a paragraph should be applied with consideration of all other relevant paragraphs.

2. In accordance with the mandate of the AMM, the Declaration is intended primarily for physicians. The AMM urges others involved in medical research in humans to adopt these principles.

General principles

3. The Geneva Declaration of the World Medical Association links the doctor with the formula "carefully and above all for the health of my patient", and the International Code of Medical Ethics states that: "The doctor must consider what is best for him. patient when giving medical attention. "

4. The duty of the doctor is to promote and ensure the health, welfare and rights of patients, including those involved in medical research. The knowledge and conscience of the doctor must be subordinated to the fulfillment of that duty.

5. The progress of medicine is based on research that, ultimately, must include studies on human beings.

6. The main purpose of medical research in humans is to understand the causes, evolution and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best tested interventions must be continually evaluated through research to be safe, effective, effective, accessible and of quality.

7. Medical research is subject to ethical standards that serve to promote and ensure respect for all human beings and to protect their health and their individual rights.

8. Although the main objective of medical research is to generate new knowledge, this objective should never have primacy over the rights and interests of the person participating in the research.

9. In medical research, it is the doctor's duty to protect life, health, dignity, integrity, the right to self-determination, privacy and confidentiality of personal information of people who participate in research. The responsibility for the protection of the persons taking part in the investigation must always rest with a doctor or other health professional and never with the participants in the research, even if they have given their consent.

10. Physicians should consider the ethical, legal and legal norms and standards for human research in their own countries, as well as current international standards and norms. A national or international ethical, legal or legal requirement should not be allowed to diminish or eliminate any measure of protection for persons participating in the research established in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research in human beings should be carried out only by persons with appropriate education, training and scientific and ethical qualifications. Research on healthy patients or volunteers requires the supervision of a physician or other appropriately qualified and qualified health professional.

13. Groups that are underrepresented in medical research must have appropriate access to participation in research.

14. The physician who combines medical research with medical care should involve his patients in the investigation only to the extent that this demonstrates a justified potential preventive, diagnostic or therapeutic value and if the doctor has good reason to believe that the participation in the study it will not adversely affect the health of those who take part in the research.

15. Appropriate compensation and treatment must be ensured for people who are injured during their participation in the investigation.

Risks, Costs and Benefits

16. In the practice of medicine and medical research, most interventions involve some risks and costs.

Medical research in humans should only be carried out when the importance of its objective is greater than the risk and the costs for the person participating in the research.

17. All medical research on human beings should be preceded by a careful comparison of the risks and costs for the individuals and groups involved in the research, compared to the foreseeable benefits for them and for other persons or groups affected by the research. the disease that is investigated.

Measures must be implemented to minimize risks. The risks must be monitored, evaluated and documented continuously by the researcher.

18. Physicians should not be involved in research studies in humans unless they are sure that the risks have been adequately evaluated and that they can be satisfactorily addressed.

When the risks involved are more important than the expected benefits or if there is conclusive evidence of definitive results, physicians should evaluate whether they continue, modify or suspend the study immediately.

Groups and vulnerable people

19. Some groups and individuals under investigation are particularly vulnerable and may be more likely to suffer abuse or additional harm.

All groups and individuals must receive specific protection.

20. Medical research in a vulnerable group is only justified if the research responds to the health needs or priorities of this group and the research can not be carried out in a non-vulnerable group. In addition, this group can benefit from the knowledge, practices or interventions derived from the research.

Scientific requirements and research protocols

21. Medical research in human beings must comply with generally accepted scientific principles and should be based on a thorough knowledge of the scientific literature, other pertinent sources of information, as well as on properly performed laboratory experiments and on animals, when appropriate. . The welfare of the animals used in the experiments must also be taken care of.

The project and the method of all study in human beings must be clearly described and justified in a research protocol.

22. The protocol should always refer to the ethical considerations that are relevant and should indicate how the principles enunciated in this Declaration have been considered. The protocol should include information on financing, sponsors, institutional affiliations, possible conflicts of interest and incentives for people in the study and information on the stipulations to treat or compensate people who have suffered damages as a result of their participation in the research.

In clinical trials, the protocol should also describe the appropriate arrangements for stipulations after the trial.

Research ethics committees

23. The research protocol should be sent for consideration, comment, advice and approval to the relevant research ethics committee before beginning the study. This committee must be transparent in its operation, must be independent of the investigator, the sponsor or any other type of undue influence and must be properly qualified. The committee must consider the laws and regulations in force in the country where the research is being carried out, as well as the

international standards in force, but they should not be allowed to diminish or eliminate any of the protections for the persons participating in the research established in this Declaration.

The committee has the right to control ongoing trials. The investigator has the obligation to provide control information to the committee, especially any serious adverse incident. No amendment to the protocol should be made without the consideration and approval of the committee. After the study ends, researchers must submit a final report to the committee with a summary of the results and conclusions of the study.

Privacy and confidentiality

24. All precautions must be taken to safeguard the privacy of the person participating in the investigation and the confidentiality of their personal information.

Informed consent

25. The participation of persons capable of giving informed consent in medical research must be voluntary. Although it may be appropriate to consult relatives or community leaders, no person able to give informed consent should be included in a study, unless they freely accept it.

26. In medical research on human beings capable of giving their informed consent, each potential individual must receive adequate information about the objectives, methods, sources of financing, possible conflicts of interest, institutional affiliations of the researcher, calculated benefits, foreseeable risks and discomforts derived from the experiment, post-study stipulations and all other pertinent aspects of the research. The potential person must be informed of the right to participate or not in the investigation and to withdraw their consent at any time, without exposing themselves to reprisals. Special attention must be paid to the specific information needs of each potential individual, as well as to the methods used to deliver the information.

After making sure that the individual has understood the information, the doctor or other appropriately qualified person should then request, preferably in writing, the informed and voluntary consent of the person. If the consent can not be granted in writing, the process to achieve it must be documented and formally attested.

All people who participate in medical research should have the option of being informed about the overall results of the study.

27. When requesting informed consent for participation in the research, the physician must take special care when the potential individual is linked to him by a dependency relationship or if he consents under pressure. In such a situation, informed consent must be requested by a properly qualified person who has nothing to do with that relationship.

28. When the potential individual is unable to give informed consent, the physician must request the informed consent of the legal representative. These people should not be included in the research that has no possibility of benefit for them, unless it aims to promote the health of the group represented by the potential individual and this research can not be carried out on people capable of giving their informed consent and research involves only minimal risk and cost.

29. If a potential individual participating in the research considered unable to give informed consent is able to agree to participate or not in the investigation, the doctor must request it, in addition to the consent of the legal representative. The disagreement of the potential individual must be respected.

30. Research on individuals who are not physically or mentally able to give consent, for example, unconscious, can be done only if the physical / mental condition that prevents the granting of informed consent is a necessary characteristic of the group investigated. In these circumstances, the doctor must request informed consent from the legal representative. If such a representative is not available and if the investigation can not be delayed, the study can be carried out without informed consent, provided that the specific reasons for including individuals with a disease that does not allow them to give informed consent have been stipulated in the protocol. of the research and study has been approved by a research ethics committee. Consent to stay in the investigation must be obtained as soon as possible from the individual or a legal representative.

31. The physician must thoroughly inform the patient about aspects of the care that are related to the investigation. The refusal of the patient to participate in an investigation or his decision to withdraw should never adversely affect the doctor-patient relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, the physician must request informed consent for collection, analysis, storage and reuse. There may be exceptional situations in which it will be impossible or impracticable to obtain consent for such an investigation. In this situation, the investigation can only be conducted after being considered and approved by a research ethics committee.

Use of placebo

33. The possible benefits, risks, costs and effectiveness of any new intervention should be evaluated by comparing it with the best interventions tested, except in the following circumstances:

When there is no proven intervention, the use of a placebo, or no intervention, is acceptable or

When for methodological, scientific and compelling reasons, the use of any intervention less effective than the best tested, the use of a placebo or no intervention is necessary to determine the efficacy and safety of an intervention.

and who receive any less effective intervention than the best tested, placebo or no intervention, will not run additional risks, serious adverse effects or irreversible damage as a result of not receiving the best intervention tested.

Great care must be taken to avoid abusing this option.

Post-test stipulations

34. Before the clinical trial, sponsors, researchers and host governments should provide post-trial access to all participants who still need an intervention that has been identified as beneficial in the trial. This information should also be provided to participants during the informed consent process.

Registration and publication of research and dissemination of results

35. Any research study with human beings should be recorded in a database available to the public before accepting the first person.

36. Researchers, authors, sponsors, editors and directors all have ethical obligations regarding the publication and dissemination of the results of their research. Researchers have a duty to

make the results of their research available to the public and they are responsible for the integrity and accuracy of their reports. All parties must accept the ethical standards of information delivery. Negative and inconclusive results must be published as well as positive results or otherwise they must be available to the public. The publication should mention the source of financing, institutional affiliations and conflicts of interest. Reports on investigations that do not conform to the principles described in this Declaration should not be accepted for publication.

Interventions not proven in clinical practice

37. When in the care of a patient the proven interventions do not exist or other known interventions have been ineffective, the doctor, after asking expert advice, with the informed consent of the patient or an authorized legal representative, can afford to use interventions not proven, if, in his opinion, it gives any hope of saving life, restoring health or alleviating suffering. Such interventions should be further investigated in order to assess their safety and efficacy. In all cases, this new information must be recorded and, when appropriate, made available to the public.

Annex 2: Certificate of Civil Liability Insurance

Don ...., representing the ....., with NIF ...., and registered office at ....., Through this document I certify:

1.- That the Center / Organization << NAME OF THE CENTER / ORGANIZATION >> has contracted a professional Civil Liability Insurance policy with the Company << NAME OF THE COMPANY >>, number << number of POLICY >>, in force and up to date with payment, in order to cover the damages that a subject may suffer as a result of the assistance activity performed by the Center / Organization,

2.- That said policy covers clinical trials of low level of intervention that, according to Royal Decree 1090/2015, of December 4, which regulates clinical trials with medicines, the Ethics Committee of Research with Medications and the Spanish Registry of Clinical Studies are those clinical trials that meet the following conditions:

- 1. The investigational drugs, excluding placebos, are authorized.

- 2nd According to the protocol of the clinical trial:

- 1st. Research drugs are used in accordance with the terms of the marketing authorization, or

- 2nd, the use of investigational medicinal products is based on evidence and is supported by published scientific data on the safety and efficacy of such investigational medicinal products in one of the Member States involved.

- 3.º The complementary diagnostic or monitoring procedures involve a risk or additional burden for the safety of the subjects that is minimal compared with that of the usual clinical practice in any of the Member States involved.

3.- That the said policy, or a similar one, will remain in force throughout the duration of the clinical trial. And for the record where it is convenient, this Certificate is issued in << City >> to << Day >> of << Month >> of << Year >>

Signed_

Annex 3: Serious Adverse Event Reporting Model

Formulario de notificación de Acontecimientos Adversos Graves ocurridos en España

NOTIFICACION DE SOSPECHA DE REACCION ADVERSA PARA MEDICAMENTOS EN INVESTIGACION	CODIGO DE PROTOCOLO (promotor): EuDract:	Nº NOTIFICACION (Promotor):
	PACIENTE Nº:	Nº NOTIFICACION

I. INFORMACION SOBRE EL ACONTECIMIENTO ADVERSO

1a. PAÍS	2. FECHA DE NACIMIENTO			2a. EDAD	3. SEXO	3a. PESO	3b. TALLA	4-4. FECHA DE INICIO DE LA REACCIÓN		
	DÍA	MES	AÑO		☐ HOMBRE ☐ MUJER			DÍA	MES	AÑO

5. DESCRIPCIÓN DEL ACONTECIMIENTO ADVERSO (Incluyendo resultados relevantes de exploración o de laboratorio, y la fecha de finalización, si procede).

Evento aparición:

ID Paciente:

Narrativa:

Evaluación:

Desenlace:

Gravedad:

Causalidad:

6-7-8. CRITERIOS DE GRAVEDAD/ DESENLACE

- ☐ FALLECIMIENTO
- ☐ LA VIDA DEL PACIENTE HA ESTADO EN PELIGRO
- ☐ HOSPITALIZACIÓN
- ☐ PROLONGACIÓN HOSPITALIZACIÓN
- ☐ INCAPACIDAD PERMANENTE O SIGNIFICATIVA
- ☐ RA CLINICAMENTE RELEVANTE

Desenlace

- ☐ PERSISTENCIA DE LA RA
- ☐ RECUPERACIÓN SIN SECUELAS
- ☐ RECUPERACIÓN CON SECUELAS
- ☐ DESCONOCIDO

II. INFORMACION DEL MEDICAMENTO

14. MEDICAMENTO SOSPECHOSO	15. DOSIS DIARIA	16. VÍA	17. ENFERMEDAD EN ESTUDIO	18. FECHAS DE: INICIO	FINAL	19. DURACIÓN DEL TRATAMIENTO

20. ¿REMITIÓ LA REACCIÓN AL SUSPENDER LA MEDICACIÓN?	20a. ¿REMITIÓ LA REACCIÓN AL REDUCIR LA DOSIS?	21. ¿REAPARECIÓ LA REACCIÓN AL ADMINISTRAR DE NUEVO LA MEDICACIÓN?
☐ SÍ ☐ NO ☐ NO PROCEDE	☐ SÍ ☐ NO ☐ NO PROCEDE	☐ SÍ ☐ NO ☐ NO PROCEDE

III. MEDICAMENTOS CONCOMITANTES E HISTORIA CLÍNICA

22. MEDICAMENTOS CONCOMITANTES (Incluyendo cosa en relación con el o los medicamentos sospechosos)	22a. DOSIS DIARIA	22b. VÍA	22c. FECHAS DE: INICIO	FINAL	22d. MOTIVO DE LA PRESCRIPCIÓN

23. DATOS IMPORTANTES DE LA HISTORIA CLÍNICA (ej. diagnósticos, alergias, embarazo, etc.)

IV. INFORMACION SOBRE PROMOTOR E INVESTIGADOR

24a. NOMBRE Y DIRECCIÓN DEL PROMOTOR	24b. NOMBRE Y DIRECCIÓN DEL INVESTIGADOR
FERRER INTERNACIONAL, S.A. Av. Diagonal, 569 08029 Barcelona	
24c. CÓDIGO DE LABORATORIO (Nº AEMPS)	24d. FECHA DEL INFORME
25a. TIPO DE INFORME ☐ INICIAL ☐ SEGUIMIENTO	25b. SE ADJUNTA INFORME COMPLEMENTARIO

Annex 4: Devicare SL letter of product donation

Barcelona, 7 de Abril de 2017

CARTA DE DEVICARE S.L. RELATIVA A LA DONACIÓN DEL PRODUCTO

Muy Sres. Míos:

Ref: ***"ENSAYO MULTICÉNTRICO, CONTROLADO Y ALEATORIZADO PARA EVALUAR EL USO COMBINADO DE UN DISPOSITIVO MÉDICO Y UN COMPLEMENTO ALIMENTICIO EN EL CONTROL DEL PH URINARIO DE PACIENTES CON UN CATÉTER DOBLE J IMPLANTADO"***

Este estudio se llevará a cabo en su centro y será coordinado por el Dr. Carles Torrecilla Ortiz.

Nuestra empresa DEVICARE S.L., con oficinas centrales en Parc de Recerca UAB, Edifici Eureka, Avinguda de Can Domènech S/N, 08193 Cerdanyola del Vallès – Barcelona, es el promotor del estudio.

Por la presente carta les confirmo de DEVICARE S.L. se compromete a facilitar GRATUITAMENTE el dispositivo *Lit-Control® pH Meter*, el complemento alimenticio *Lit-Control® pH Down* y el *placebo,* a los pacientes reclutados en el estudio durante todo el tiempo que dure la intervención.

Los complementos que se administrarán en el estudio cumplen con la normativa actual en materia de complementos alimenticios *Directiva 202/46/CE*.

Si necesitara más información sobre este punto, estoy a su entera disposición.

Atentamente les saluda,

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Director general/Responsable
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Annex 5: Technical Sheet of the Product under investigation (available in the researcher's manual)

Annex 6: Blockage Risk Factor (Clifford, 2002)

Assessment		1		2		3
Reason for catheter	Surgical		Incontinent		Obstruction	
Patient mobility	Mobile		Wheelchair		Immobile	
Mental state	Alert		Confused		Disorientated	
Daily fluid intake	3 litres		2–3 litres		1–2 litre	
Bowels	Daily		Occasional constipation		Constipated	
Drainage system	Valve Link		Other			
Catheter care	Self caring		Carer		Other	
History of blockage	None		Monthly		Frequently	

Score: Low risk 8–11
Medium risk 12–15
High risk 16+

Table extracted from Rigby, Deborah. "pH testing in stent maintenance: the clinical debate." (2004).

Annex 7: Degree of calcification (Urdiales-Ortiz A, et al., 2012).

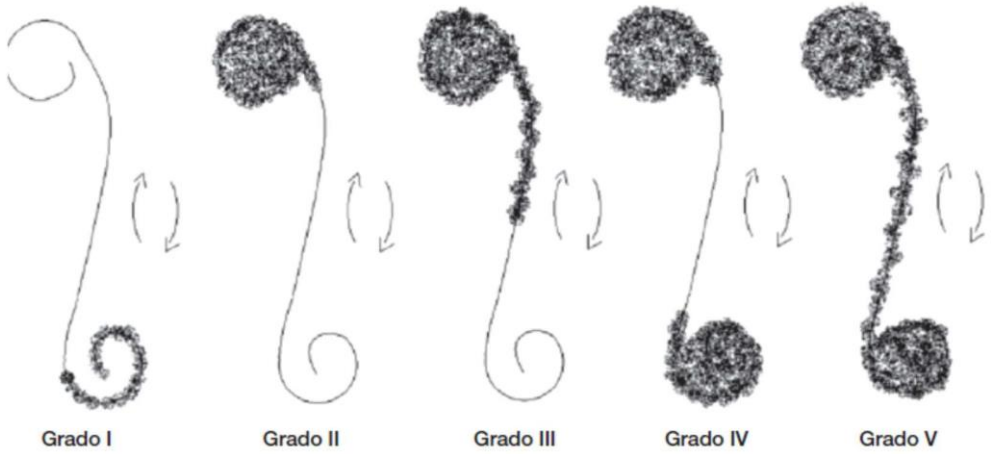

Figura 1. Sistema de clasificación FECal (*Forgotten, Encrusted and Calcified*) para catéteres ureterales.

Figure extracted from Urdiales-Ortiz A, et al. (2012). Laparoscopic double J calcified stent in a patient with thrombocytopenic purpura.

Annex 8: Metabolism of L-methionine (Hesse A, & Heimbach D; 1999)

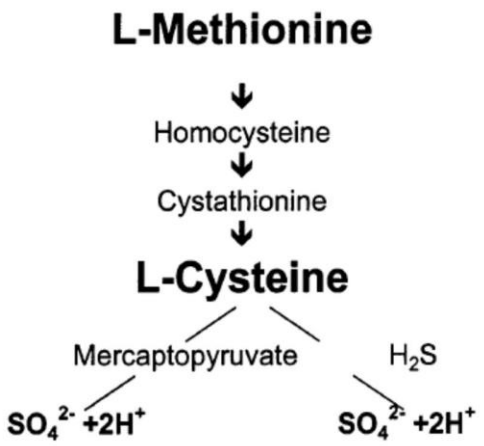

Fig. 7 Metabolism of L-methionine

Figure extracted from Hesse, A., & Heimbach, D. (1999). Causes of phosphate stone formation and the importance of metaphylaxis by urinary acidification: a review. World journal of urology, 17 (5), 308-315.