# INFORMED CONSENT FORM

**TITLE:** Randomised clinical trial to evaluate the dose and administration time of Indocyanine Green in Near-Infrared Fluorescein Cholangiography during laparoscopic cholecystectomy.

**CODE:** DOTIG Trial.

**EudraCT number**: 2022-000904-36.

**Version**: 2.0.

**Sponsor:** Biomedical Research Institute of Salamanca (IBSAL).

**Principal Investigator:**

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## INTRODUCTION

We are writing to inform you about a research study in which you are invited to participate. Our intention is that you receive correct and sufficient information so that you can decide whether or not to participate in this study. To do so, please take the time to read this information sheet carefully and thoroughly and discuss it with whomever you feel appropriate. Ask your doctor or the study staff to explain any words or information that you do not understand clearly, as well as any questions you may have.

If you decide to participate, we will ask you to sign the attached informed consent form. We will provide you with an original copy of this signed and dated document for you to keep and the original document will be kept on file with the rest of the study documentation.

The study has been approved by the Ethics Committee for Research of the University Hospital of Salamanca, in accordance with current legislation, Royal Decree-Law 1090/2015, which regulates clinical trials with medicines, the Ethics Committees for Research with medicines and the Spanish Register of Clinical Studies, Royal Decree-Law 1591/2009 regulating medical devices, Royal Decree-Law 1616/2009 on active implantable medical devices (if applicable), and Circular 7/2004 of the Spanish Agency for Medicines and Medical Devices on clinical research with medical devices.

It has also been designed and will be conducted in accordance with the recommendations set out in the Declaration of Helsinki and the Standards of Good Clinical Practice.

You should be aware that your participation in this study is voluntary and that you may decide NOT to participate. If you decide to participate, you may change your decision and withdraw your consent at any time, without altering your relationship with your doctor or harming your health care.

You should also be aware that you may be withdrawn from the study if the sponsor or investigators deem it appropriate, either for safety or other reasons. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

**AIM OF THE STUDY**

You are invited to participate in the study because you have been diagnosed with symptomatic gallstone disease. The gold standard treatment for your disease is the removal of the gallbladder (cholecystectomy), ideally by minimally invasive approach (laparoscopy).

To avoid some of the complications of laparoscopic cholecystectomy, the use of a tool called near-infrared fluorescein cholangiography has recently been developed. This technique attempts to fluorescently map critical anatomical structures that appear during surgery, using a substance called indocyanine green. This drug is usually administered intravenously and is eliminated through the bile. Thanks to the fluorescent characteristics of indocyanine green, and its biliary elimination, we will be able to obtain real-time and accurate images of the extrahepatic biliary anatomy. This will aid intraoperative anatomical identification and may prevent injury to important structures. However, the administration time and the ideal dose of indocyanine green to obtain an accurate technique is currently not defined. The DOTIG trial (dose and administration time of indocyanine green in near-infrared fluorescein cholangiography during laparoscopic cholecystectomy) will attempt to find the optimal dose and ideal administration time for performing laparoscopic cholecystectomy with fluorescein cholangiography.

**STUDY PROCEDURES AND POSSIBLE RISKS AND DISCOMFORTS**

All patients that meet the inclusion criteria and have an indication of a laparoscopic cholecystectomy are eligible upon agreement to participate in this study. You will not be able to participate in this study if you have any of the following contraindications: being a minor, pregnancy or breastfeeding at the time of surgery, advanced chronic kidney disease, allergies or adverse reactions to the product, its excipients, to iodinated contrasts or some diseases of the thyroid gland.

The total number of patients planned to be included in the study is 200 subjects. The drug to be administered is called Verdye (Diagnostic Green GMBH, Aschheim-Dornach, Germany) and contains indocyanine green sodium. All patients who agree to enter the study will be administered the drug intravenously at a variable dose and interval prior to surgery. The study will have four treatment groups divided into different doses and times. The doses will be calculated as a fixed dose or a weight-adjusted dose. The administration interval will vary from the time of admission

to the hospital ward to the time of anaesthetic induction. Assignment of the dose and time of administration prior to surgery will be randomised using a computer application.

No biological samples will be collected for research purposes and no procedures or tests will be performed that are not part of routine clinical practice.

All information about this study will be stored in encrypted form, and will be used exclusively for the purposes specified here. In the event that your data is transferred to other research groups, this will always be done in accordance with current legislation, keeping your data coded, in order to carry out studies related to the objectives of this work, and with prior authorisation from the Research Ethics Committee. In the event that the objectives of the research work proposed by other research groups are different from those of the present project, a new consent will be requested.

Indocyanine green (Verdye) is a product authorised by the Spanish Agency of Medicines and Medical Devices (AEMPS) and the European Medicines Agency (EMA). It has been marketed since 2017 for hospital use only and in authorised diagnostic centres. Indocyanine green is approved for diagnostic use in the field of heart, brain, eyeball and liver studies. The drug has been widely used for fluorescein cholangiography since the first study was published in 2009 to the present day. It has been shown to be safe in humans, with a very low rate of adverse events. As a drug approved by the competent health authorities, information on the side effects of indocyanine green (Verdye) is available to everyone. There may be side effects or reactions that you should be aware of. Severe allergic reactions (anaphylaxis) are extremely rare (affecting less than 1 in 10,000 patients). Patients with kidney disease may be more at risk of developing allergic reactions. Only two cases of death have been reported with the use of indocyanine green during cardiology studies (frequency less than 1/330,000 estimated cases). Cases of indocyanine green overdose are unknown at present. No additional risks are foreseen as you will not undergo any procedures outside of standard clinical practice.

You as a study participant will be expected to comply with a number of responsibilities as outlined below:

- Compliance with the scheduled visit during the first postoperative month.
- Report any adverse events or changes in medication, advising that, except in an emergency, do not change the medication you are taking or take other medications or "herbal medicinal products" without first consulting with the study doctor.

Please speak to your study doctor for a complete list of side effects reported with this drug and in any case, if you wish, you will be given the package leaflet for both drugs.

**Voluntary participation and withdrawal**

You are free to decide whether or not you wish to take part in this study, participation is entirely voluntary. If you decide to participate, you still have the possibility to withdraw at any time, without having to give any explanation, and without any penalty or negative consequences for you. If you change your mind about your data, you have the right to request its destruction or anonymisation, through your doctor/researcher. However, you should be aware that the data obtained in the analyses carried out up to that point may be used for the purposes requested and may be retained in compliance with the relevant legal obligations.

**Potential benefits**

No direct benefit is expected from your participation in the study. However, the information obtained from this research project may contribute to medical progress and may help other patients in the future. You will not receive any financial benefit from the donation of the samples and the release of the data provided, nor will you have any rights to potential commercial benefits from any discoveries that may be made as a result of the research conducted.

**Alternative treatments**

If you do not participate in the study, you will receive treatment according to standard clinical practice.

**Data protection and confidentiality**

All information about your results will be treated in the strictest confidence. Both the centre and the sponsor and research team are responsible for the processing of your data and undertake to comply with the data protection regulations in force, currently Organic Law 3/2018, of 5 December, Protection of Personal Data and Guarantee of Digital Rights and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (RGPD). The data collected for the study will be identified by a code, so that no information that can identify you is included, and only the research team will be able to relate this data to you. Therefore, your identity will not be disclosed to any other person except to the health authorities, when required or in cases of medical emergency. Research Ethics Committees, representatives of the Health Inspection Authority and personnel authorised by the sponsor may only have access to verify personal data, clinical trial procedures and compliance with the standards of good clinical practice (while maintaining the confidentiality of the information).
Your data will be kept under appropriate security conditions and it is guaranteed that subjects cannot be identified through means considered reasonable by people other than those authorised. The research team will analyse your data based on the legitimate interest of achieving

the purposes of the study. The Investigator and the Sponsor are obliged to retain the data collected for the study for at least 25 years after completion of the study. Thereafter, your personal information will only be retained by the facility for your health care and by the research team for other scientific research purposes if you have given your consent to do so and if permitted by applicable law and ethical requirements.

If the results of the study are likely to be published in scientific journals, no personal data of the participants in this research will be provided at any time. We inform you that you have the right to access, rectify or cancel your data, and you may limit the processing of data that are incorrect, request a copy or that the data you have provided for the study be transferred to a third party. To exercise your rights, or in the event that the participant wishes further information about the processing of your personal data, you may contact the principal investigator of the study whose details are specified at the end of this document, the Data Protection Officer of the Regional Health Authority (dpd@saludcastillayleon.es) or our site (protecciondedatos@ibsal.es). We remind you that the data cannot be deleted, even if you stop participating in the trial in order to ensure the validity of the research and to comply with legal obligations. You also have the right to contact the Data Protection Agency if you are not satisfied.

**Information on results**

At your request, at the end of the study and in accordance with article 27 of the Law 14/2007 on Biomedical Research, you may be provided with information about the results of this research study.

I consent to the future use of the data collected in this research study to carry out other research related to the medical speciality or research area of this study.

YES / NO

I consent to future re-accessing of my medical records to collect data deemed important for further research related to the medical specialty or research area of this study.

YES / NO

Contact details of the research team:

If you have any questions or need further information, please contact:
**Name**: Jaime López Sánchez
**Telephone**: +34 923291100

Whatever your decision, both the promoter and the research team would like to thank you for your time and attention.

**INFORMED CONSENT**

I (Name and Surname) _____

I have read the information sheet I have been given about the study.

I have been able to ask questions about the study.

I have received sufficient information about the study.

I have read the information sheet given to me.

I have spoken to the Researcher _____ I understand that my participation is voluntary.

I understand that I can withdraw from the study:

1. Whenever I want to.
2. Without having to explain myself
3. Without any negative repercussions

I voluntarily agree to participate in the clinical trial and authorise the use of all information obtained. I understand that I will receive a signed copy of this informed consent form.

Participant's signature Date

Name and signature of the researcher Date

Signature of legal representative, family member or person related in fact Date