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The Cleveland Clinic Foundation
Consent to Participate in a Research Study

Study Title: Randomized Controlled Trial: Liposomal Bupivacaine (Exparel®) versus Bupivacaine Hydrochloride versus Placebo for TAP blocks during Open Retromuscular Ventral Hernia Repair

Principal Investigator: Michael J. Rosen, MD (216) 445-3441

You are being invited to participate in a research study. A research study is designed to answer specific questions about new ways to prevent, detect, and treat disease. Being in a research study is different from being a patient. The purpose of this document is to provide a written summary of the discussion and exchange of research information you had with the research team. It is also for use as a reference during the study.

Please note:

- **You are being asked to participate in a research study**
- **Ask as many questions as needed so you can make an informed decision.**
- **Carefully consider the risks, benefits, and alternatives to the research**
- **Your participation is completely optional and will have no effect on the quality of your medical care if you choose not to participate. You can also withdraw from the study at any time.**

1. INFORMATION ON THE RESEARCH

Why are you being asked to take part in this research?
You are being asked to participate in a clinical research study because you are scheduled to undergo repair of your ventral hernia as part of your medical care.

Why is the research study being done?
Patients usually experience some level of pain after their hernia repair. To control pain after the operation, your doctor has many options. One of them is to make some injections of pain blocker medications into the nerves that are responsible for the sensations of your abdominal wall.This procedure is called TAP block (transversus abdominis place block). These medications are called local anesthetics, and there is a variety of medications that can be used. One of such medications is called Exparel® (Liposomal Bupivacaine). Exparel® has the potential benefit of lasting more hours than regular anesthetics. Although this drug is being used with increasing frequency, we do not have good quality studies investigating the benefits of using this medication during a hernia repair, especially when compared to other types of local anesthetics (Bupivacaine Hydrochloride) or when compared to not injecting this medication at all. We want to do this study to see if Exparel®, when injected in the nerves of your abdominal wall during the operation can: (1) reduce the dose of additional painkillers needed to achieve good pain control after surgery and (2) reduce the pain levels after your ventral hernia operation. We want to

compare Exparel® to using regular local anesthetics (Bupivacaine Hydrochloride) or when using no active drug (saltwater) for these injections.

It is important to note that, regardless of whether a patient will receive injections of Exparel®, a regular anesthetic (Bupivacaine Hydrochloride) or placebo (water) during the study, all patients will receive other pain medications after the operation to make sure they have good pain control after the operation. Therefore, this study is to evaluate if Exparel® plus other medications for pain is better than the other medications alone. All patients are expected to receive adequate pain control after the operation.

How many people will take part in this study?
Approximately 162 patients will be enrolled in this study at the Cleveland Clinic. 54 patients are expected to receive Exparel®, 54 patients are expected to receive regular local anesthetics (Bupivacaine Hydrochloride), and 54 patients are expected to receive placebo (water) during the operation.

What is involved if you decide to take part in this research study?

Today will be your first meeting with your surgeon. During this visit, your surgeon will evaluate your ventral hernia and determine if you are a surgical candidate for ventral hernia repair. If your surgeon believes that you are a candidate for ventral hernia repair, he/she will discuss this with you. Also, your surgeon will ask you a few questions about your health to check if you might be a candidate to participate in this study. Those questions are mainly related to whether you have any disease that causes you chronic pain which would cause you to use opioid painkillers daily, or if you have any health problems that will limit you in participating in this study.
If your surgeon thinks you are eligible to participate in the study, he will discuss that with you and will invite you to participate. Also, your surgeon will also answer any questions you may have about the reasons to do this study, the study procedures and the risks in participating in this study. If you agree to participate in the study and sign this written consent form, your active participation in this study will last for 1 month and will be divided into tasks to be completed before the operation, tasks to be completed after the operation, during your hospital stay, and tasks to be completed after the operation during your follow-up visit.

Before the operation (Preoperative Visit)

Basic information about your health will be collected, and physical examination will be performed. These are consistent with the routine care and are not part of the study.
You will receive routine preoperative care, which will be personalized for each patient. This routine care is also not part of the study.
As part of this study, you will be asked to fill out 2 questionnaires related to your quality of life and current pain levels related to your hernia. Filling these questionnaires will not take you more

than 5 to 10 minutes. Also, your doctor will ask you a few questions regarding the use of painkillers now or in the past.

On the Day of the Operation (Randomization)

If you participate in this study, you will be assigned to a study group by chance using a process similar to the flip of a coin. This process is called randomization and will happen on a computer. This means that 1/3 of the people in this study will get injections of Exparel® during the operation, 1/3 of the people in this study will get injections of regular local anesthetic (Bupivacaine Hydrochloride), and 1/3 of patients will get injections of normal saline (saltwater/placebo). Randomization will occur during your surgery. This means that no one will know what treatment you will get prior to the time of operation. Your operation will be performed as usual, and according to what was previously discussed by your surgeon and you and the surgery itself is not part of this study. You will not be allowed to know what type of medication you were assigned to receive until completion of the study. However, this information can be obtained if you have a medical emergency.

Again, we would like you to remember that, even though patients will have different drugs injected, all patients will receive other types of pain medications after the operation, to ensure you have adequate pain control. The most important method of pain control after the operation will be a device that is called "patient-controlled analgesia," where patients can press a button everytime they feel pain, and the machine will administer a dose of pain medication intravenously. Also, you will get other pain medications by mouth as prescribed by your doctor. Therefore, we will be investigating if adding Exparel® will result in any benefits when compared to the standard methods for pain control alone.

During your hospital stay

While you are in the hospital, for several times, a member of the research team will ask you about your pain levels at that exact moment, on a scale from 0 (no pain) to 10 (worst pain imaginable). You will be asked to mark on a paper, the level of your pain at that moment. We will record your answers. Also, we will record the total amount of opioid painkillers you have used to achieve good pain control during all your hospital stay.

After your hospital discharge

You will be given instructions to return for a follow-up visit with your surgeon, between 15 and 45 days after your operation, and we expect that you come in person to be seen by your doctor at the General Surgery Clinic. This time period for follow-up is standard of care, and this visit is expected to happen independently of your participation in this study. You will have your incisions and wounds evaluated and examined for general health and hernia recurrence. You will be asked about any medications you are taking and about any problems you may have had with

your ventral hernia repair. In addition to standard of care procedures, you will be asked to complete the same surveys that you filled out prior to surgery at this visit. You can be informed whether you received Exparel®, Bupivacaine Hydrochloride or Placebo at the time of your 30-day follow-up appointment.

How long will you be in the study?
Your participation in this study will last for 30 days (±15 days) from the date of your original ventral hernia repair surgery. You can choose to stop participating at any time without penalty or loss of routine perioperative surgical care to which you are entitled. However, if you decide to stop participating in the study, it is important you talk with your doctor first.

2. ALTERNATIVES

What are the alternatives to participation in the research study?
Your participation in this study is completely voluntary. You do not have to take part in this study if you do not want to participate or if you feel uncomfortable with any part of the aforementioned process. Your choice to participate or not will have no impact on the clinical care you will receive from your doctor. This means that you do not need to participate in this study to have your hernia fixed. Should you decide to take part and later change your mind, you can do so at any time. Again, withdrawing from this research study will have no impact on the clinical care you will receive from your doctor.

3. RISKS

What are the risks of participating in the research study?
Questionnaires: It is possible that some of the questions may be upsetting or you may feel uncomfortable answering them. If you do not wish to answer a question, we can skip this question.

Personal Health Information: Safeguards are in place to protect your information. Data will be stored on a password-protected computer at Cleveland Clinic that is accessible only to the study staff. Also, your personal information will be stored in two different protected databases: one is called the AHSQC (Americas Hernia Society Quality Collaborative), and the other one is called RedCAP (Research Electronic Data Capture). Although we ensure that will take all the precautions to make your information protected, there is a small risk to the confidentiality of your data.

Exparel®: Side effects can occur with any medication; it is important not to ignore anything you might feel. Some patients in clinical trials who received Exparel® or other pain relievers experienced nausea, vomiting, and/or constipation. Speak with your doctor right away if you get any of these more frequent side effects, or if you have questions about possible side effects.While some publications have shown a decrease in pain immediately following operation with Exparel® use, this medication does have over a 10% rate of nausea, vomiting, and constipation. There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesias. Neurologic reactions are characterized by excitation and/or depression. Excessive doses of bupivacaine solution such as Exparel can lead to cardiac arrhythmias (disregulated heart beats) and sometimes leading to

death. Although these effects can occur, they are very rare. For more information, please visit www.EXPAREL.com or call 1-855-RX-EXPAREL (793-9727).

Bupivacaine Hydrochloride: Side effects of regular local anesthetics include: nausea, vomiting, chills, headache, restlessness, anxiety, dizziness, ringing in ears or blurred vision. Again, even those are not very frequent; it is important not to ignore anything you might feel and let your doctor know right away if you experience any of this symptoms.

TAP blocks: TAP blocks are a safe procedure and complications are extremely rare but can include bruising on your back, allergy or toxicity to the local anesthestic administered (either Exparel or Bupivacaine Hydrochloride). In this instances, you would experience the symptoms listed in the previous paragraphs. Again, it is extremely important that you inform your doctor and the first caregiver you have contact if you experience any of these symptoms.

4. BENEFITS

What are possible benefits of participating in the research?

If you agree to take part in this study, you may or may not have a direct medical benefit. We hope the information learned from this study will benefit medical science and provide information which may help improve the field of ventral hernia surgery and pain control after major abdominal operations.

5. COSTS

There will be no additional costs to you as a result of taking part in this study. However, routine medical care for your condition (the care you would receive whether or not you were in this study) will be charged to you and/or your insurance company. You will be responsible for any co-payments and deductibles that are standard for your insurance coverage. The cost of each of the interventions (Exparel®, Bupivacaine Hydrochloride and Placebo) is different. In case you are assigned to receive Exparel®, the cost of the drug will be covered by Pacira Pharmaceuticals, therefore, neither you nor your insurance will be responsible for this expenditure. In case you are assigned to receive Bupivacaine Hydrochloride or Placebo (salt water), the costs for each of this interventions (Bupivacaine US$ 2 and Saline US$1, approximately) will be billed to you or your insurance as part of your routine care.

6. COMPENSATION

Are there any payments to you if you participate in this study?

There are NO payments to you should you decide to participate in this study.

7. RESEARCH RELATED INJURY

What will happen if you are injured as a result of taking part in the research?

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We do not expect that anyone will be injured by participating in this research. Exparel is a drug approved by the FDA and will be used for this study according to the proper recommendations. Nevertheless, in the event that you are injured as a result of participation in this research, medical care is available to you. The costs of such medical care will be billed to you or your insurance company. There are no plans to provide compensation for lost wages, direct, or indirect losses. The Cleveland Clinic will not voluntarily provide compensation for research-related injury. You are not waiving any legal rights by signing this form. Further information about research related injury is available by contacting the Institutional Review Board at (216) 444-2924.

8. PRIVACY AND CONFIDENTIALITY

What will happen to your information that is collected for this research?

Cleveland Clinic has rules and procedures to protect information about you. Federal and State Laws also protect your privacy.

The research team working on the study will collect information about you. This includes your health information, data collected for this research study, and personal identifying information including your name, address, social security number, date of birth, and other identifying information. This information will be used for the stated purpose of the study.

Generally, only people on the research team will know your identity and that you are in the research study. However, sometimes other people at Cleveland Clinic may see or give out your information. This includes people who review research studies including the Institutional Review Board and Research Compliance, their staff, lawyers, or other Cleveland Clinic staff. If you agree, your personal physician may be informed of your participation in the study.

People outside of Cleveland Clinic may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration) and safety monitors. Cleveland Clinic will take steps to ensure your information is kept confidential and that only the health information that is minimally required to conduct the study is used or disclosed to people outside Cleveland Clinic. However, people outside Cleveland Clinic who receive your information may not be covered by this promise.

You do not have to give us permission to use and give out your information. However, you will not be able to participate in this research study without providing this permission by signing this consent form. The use and disclosure of your information have no expiration date.

You may cancel your permission to use and disclose your information at any time by notifying the Principal Investigator in writing (Michael Rosen MD, 9500 Euclid Avenue, Cleveland, Ohio 44195). If you do cancel your permission to use and disclose your information, your participation in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study.

9. RESULTS

What will happen to the results of this study?

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A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.
If the results of this study are published, your identity will remain confidential.

10. CONFLICT OF INTEREST

Do the researchers or institution have any conflicts of interest relating to this study?
Yes.

1. Dr. Michael J. Rosen is the Founder and Chief Executive Officer of the Americas Hernia Society Quality Collaborative (AHSQC) Foundation – which is the database that will collect much of your information. He receives a salary for these services. The AHSQC will receive and store data collected as part of this research project.
2. Pacira Pharmaceuticals, the company that produces Exparel®, will also be providing the institution a research grant to cover the expenses related to this research, and as previously explained, will cover the expenses related to Exparel® for the individuals who are assigned to receive this intervention. This is not a compensation for any of the study members to conduct this research.

These financial interests are being managed and are within permissible limits established by the Cleveland Clinic's Conflict of Interest Policy. If you have any questions regarding these conflicts of interests, please ask your doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924.

11. QUESTIONS

Who do you call if you have any questions or problems?
If you have any questions, concerns, or complaints about the research or develop a research-related problem, contact Michael J. Rosen, MD at (216) 445-3441 during regular business hours (8am-5pm). After hours, please call the clinic operator at (216) 444-2000 or (800) 223-2273 and ask for the General Surgery resident on call. If you have questions about your rights as a research subject, you may contact the local Cleveland Clinic Institutional Review Board at (216) 444-2924.

12. VOLUNTARY PARTICIPATION

What are your rights as a research participant?
Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to withdraw from the study, you should discuss with your study doctor your decision to ensure a safe withdrawal.

You may refuse to be in or remove yourself from the study at any time without providing a reason, and this will not affect the standard of care you receive. To withdraw from the study, tell

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the principal investigator you no longer want to participate by contacting Michael Rosen, MD at 216-445-3441 or rosenm@ccf.org.

If you choose to withdraw from the study, you will be followed based on the standard of care at the institution. The investigator can remove you from the study without your approval. Possible reasons could be if participation appears to be medically harmful to you, if it is discovered that you do not meet eligibility requirements, or if the study is canceled.

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13. SIGNATURES

Statement of participant

I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. Signing this form does not waive any of my legal rights. I understand that a signed copy of this consent will be provided to me. By signing below, I agree to take part in this research study.

_____
Printed Name of Participant

_____ _____
Participant Signature Date

Statement of person conducting informed consent discussion

I have discussed the information contained in this document with the participant, and it is my opinion that the participant understands the risks, benefits, alternatives, and procedures involved in this research study.

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date