Consent to Participate in Research

Title of Research Project:	Phase I evaluation of the safety, reactogenicity and immunogenicity of fractional-dose inactivated polio vaccine (fIPV) given intradermally with double mutant [LT(R192G/L211A)] Enterotoxigenic *Escherichia coli* heat labile toxin (dmLT) adjuvant
Co-Principal Investigators:	Beth Kirkpatrick, MD, Kelly Cowan, MD
Sponsor:	University of Vermont Vaccine Testing Center UVM Larner College of Medicine 89 Beaumont Avenue, Given C205 Burlington, VT 05405

Introduction

You are being invited to take part in this research study because you received the usual doses of inactivated polio vaccine (IPV) and no oral polio vaccine (OPV) as a child.

This study is being conducted by the University of Vermont (UVM) at the UVM Clinical Research Center at UVM Medical Center and Vaccine Testing Center.

We encourage you to ask questions and take the opportunity to discuss the study with anybody you think can help you make this decision.

Key Information to Help You Decide Whether or Not This Study Is Right for You

- Polio is an infection that can cause paralysis and death. It is preventable with a vaccine. This study is being done because a better polio vaccine is needed to help completely end polio disease around the world.
- This study will test whether adding a substance named dmLT to a regular polio vaccine will be as safe as the regular polio vaccine by itself. This study will also test whether dmLT helps the vaccine work better.
- Volunteers will get one injection of polio vaccine OR one injection of polio vaccine mixed with dmLT. The injection will be given below the outer skin layer in the upper arm.
- The study will last for a year. There will be 5 scheduled clinic visits in the first 28 days of the study. Volunteers will have blood draws at all of the visits and give a stool sample for 2 of the visits. Then volunteers will get a phone call once a month for the next 11 months.
- The most common risks of the study include pain, tenderness, redness, swelling, itching, and change in skin color at the injection site. We will also ask about fever, nausea, vomiting, diarrhea, abdominal pain, low appetite, headache, rash, muscle aches, and joint pain.
- You cannot get a polio infection from being in this study.
- It is up to you whether you choose to participate in this study. There will be no change in your usual medical care if you choose not to participate.

The information above is only a brief summary of the study. If you are interested in learning more, it is important to read the following pages for additional detailed information about the study. If you decide to take part in the research, you will be asked to provide written consent at the end of this document.

Why Is This Research Study Being Conducted?

Polio is a serious disease that can cause paralysis and death. It is caused by a virus and can be prevented by vaccine. The World Health Organization's (WHO) Global Polio Eradication Initiative is trying to get rid of all polio disease around the world. Researchers want to help by testing a new vaccine.

In many countries, people are vaccinated with oral polio vaccine (OPV) given by mouth during childhood. OPV is good at giving immunity (protection from polio) in the body and the gastrointestinal (GI) tract. Immunity in the GI tract is called mucosal immunity. The downsides of using OPV are that it can be shed into the environment in people's feces after vaccination where it can infect people who are not vaccinated, and it can cause paralysis in 2-4 of every one million children vaccinated with OPV. The United States (U.S.) stopped giving any OPV to people for vaccinations in the 1990's. Since then, a polio vaccine called inactivated polio vaccine (IPV) is given as an injection for routine childhood immunizations in the U.S. You cannot get polio infection from IPV and it will not be shed into the environment.

In 2016, the WHO started a plan to help other countries gradually get rid of OPV. The downside of using IPV by itself is that, unlike OPV, it doesn't give enough mucosal immunity to protect people living in places where there is still polio. There are also supply shortages of IPV, which is a problem if there are outbreaks of polio. For the supply of IPV to help more people, it is safe and effective to use a tiny dose of IPV injected under the top layer of skin (intradermal or ID injection) rather than getting the full dose in the muscle. This is called a fractional dose of IPV, or fIPV.

To help stop using OPV globally, a better fIPV vaccine is needed. fIPV vaccine needs a substance to help stimulate a mucosal immune response. dmLT is a substance that has been shown to stimulate a mucosal immune response. It has been shown to be safe and effective in both humans and animals, both by itself and when given with other vaccines.

This study will test a mixture of fIPV-dmLT given intradermally (under the outer layer of the skin). This is the first study done in humans to give this combination intradermally. The IPV vaccine has already been approved by the FDA. The fIPV-dmLT vaccine has not been approved by the FDA.

Adults in the US who have received the recommended IPV childhood vaccines and no OPV are able to be volunteer for this study. The study will randomly select participants to receive either a fractional dose of fIPV with dmLT or a dose of fIPV alone.

30 volunteers will be in the study. On the day of vaccination we will ask additional individuals to volunteer as alternates. The alternates will be asked to attend dosing day, but do not receive vaccine unless any of the 30 volunteers change their mind or cannot participate on dosing day. Alternates who do not receive vaccine on dosing day 0,may still be eligible to receive vaccine at a later dosing day. 20 volunteers will receive one intradermal injection of fIPV-dmLT and 10 volunteers will receive one intradermal injection of fIPV alone. Volunteers, researchers, and the person giving the vaccine will not know which vaccine is being given. This is referred to as a randomized, blinded clinical trial. It is twice as likely that volunteers will receive fIPV-dmLT. We will carefully monitor you for side effects from the vaccine, and blood and stool tests will be done to look at your immune response to the vaccine.

The goals of this study are to:

- Determine the safety fIPV-dmLT vaccine. This is done by documenting side effects both in the short term and long term.
- Measure immune responses to fIPV-dmLT compared to fIPV. This is done by measuring the immune system response by blood and stool tests.

What Is Involved In The Study?

- If you choose to participate in this 1 year long study, you will have a screening visit to determine if you are eligible, then 5 in-person clinic (study) visits in the first 28 days, followed by 11 phone calls that happen once per month.
- Clinic visits are outpatient at the University of Vermont Medical Center in the Clinical Research Center.
- The first study visit will last approximately 2 hours. The next 4 visits (ending at the 28 day visit) will last approximately 1 hour each. Monthly phone calls will take approximately 15 minutes each.
- There are blood draws at each of the 5 in-person clinic visits. Topical anesthetic cream may be used to numb the area where blood will be drawn, but this is optional.
- Stool samples will be collected at 2 visits (the first and last study visits). You will be given a stool collection kit to bring the stool sample in from home or you can give the stool sample during the visit.
- You will keep a symptom diary for the first week after you receive the vaccine or until any side effects have resolved or are stable.
- The study schedule is detailed below.

Screening visit

- Decide if you want to be in the study (Informed Consent)
- You will answer questions about your understanding of the consent form and get a copy of the signed consent form, if you agree to participate
- You will bring in your immunization record and it will be reviewed by a member of the study team to confirm that you have documentation that you received the routine childhood IPV vaccines and no childhood oral polio vaccine
- You will be asked for your medical history and list of current medications
- You will have a physical examination

- Your vital signs will be measured (height, weight, blood pressure, heart rate, respiratory rate)
- You will have approximately 8ml (1.5 teaspoons) of blood drawn
- Females will be asked to use an effective form of birth control to avoid becoming pregnant at least for 30 days before receiving the vaccine and for 28 days after receiving the vaccine.
- You will receive a take-home kit for stool sample collection for the first study visit.

If you are eligible and sign the consent form at the screening visit, you will be invited to participate in the study. We will ask you to return for vaccine dosing, Day 0, for study enrollment.

First study visit (Day 0)
- You will be asked for your medical history and list of current medications
- You will have a physical examination
- Your vital signs will be measured (blood pressure, heart rate, temperature, respiratory rate)
- Females will have a urine pregnancy test and will be asked to use an effective form of birth control to avoid becoming pregnant in the first 28 days of the study. If you are pregnant you cannot be in the study.
- You will have approximately 62.5 ml (about 4.3 tablespoons) of blood drawn
- You will give a stool sample (brought in from home or done in clinic).
- You will receive one dose of either fIPV or fIPV-dmIT vaccine intradermally (injected just below the outer layer of skin) in the upper arm.
- You will be observed for 30 minutes after getting the vaccine.
- You will receive a 7 day symptom diary card to record adverse events. You will receive education on signs and symptoms of potential adverse events, and how and when to contact study staff.

Second study visit (Day 1)
- Changes in your medical history or medications will be reviewed
- You will have an exam of the injection site
- Your vital signs will be measured (blood pressure, heart rate, temperature, respiratory rate).
- If you are having any possible vaccine side effects, you may have a physical exam to focus on that problem
- Pregnancy prevention will be reviewed for females of child-bearing potential
- You will have approximately 25 ml (about 1.7 tablespoons) of blood drawn
- Your symptoms diary card will be reviewed and adverse events (unwanted effects) will be discussed

Third study visit (Day 7)
- Changes in your medical history or medications will be reviewed
- You will have an exam of the injection site
- Your vital signs will be measured (blood pressure, heart rate, temperature, respiratory rate).
- If you are having any possible vaccine side effects, you may have a physical exam to focus on that problem

- Pregnancy prevention will be reviewed for females of child-bearing potential
- You will have approximately 48 ml (3.2 tablespoons) of blood drawn
- Your symptoms diary card will be reviewed and adverse events will be discussed. If you have an adverse event recorded on day 7, you will be given a second 7 day diary card to record symptoms

Fourth study visit (Day 10)
- Changes in your medical history or medications will be reviewed
- You will have an exam of the injection site
- Your vital signs will be measured (blood pressure, heart rate, temperature, respiratory rate).
- If you are having any possible vaccine side effects, you may have a physical exam to focus on that problem
- Pregnancy prevention will be reviewed for females of child-bearing potential
- You will have approximately 40 ml (2.7 tablespoons) of blood drawn
- Adverse events will be discussed. If you still have a symptom diary, it will be reviewed. If you are still having symptoms, a plan will be made to follow them up until they resolve or are stable.
- You will receive a take-home kit for stool sample collection for the day 28 visit.

Fifth visit (Day 28) – last in-person study visit
- Changes in your medical history or medications will be reviewed
- You will have an exam of the injection site
- Your vital signs will be measured (blood pressure, heart rate, temperature, respiratory rate).
- If you are having any possible vaccine side effects, you may have a physical exam to focus on that problem
- You will have approximately 10 ml (0.7 tablespoons) of blood drawn
- You will give a stool sample (brought in from home in kit or done in clinic).
- Adverse events will be discussed. If you still have a symptom diary, it will be reviewed. If any adverse events are ongoing we may need to arrange for either phone or in-person follow-up earlier than the scheduled monthly call.

Monthly phone followup (11 phone calls, starting 1 month after the 28 day visit)
- Changes in your medical history or medications will be reviewed
- Adverse events will be discussed

Unscheduled visits
If there is an adverse event that requires a clinic visit for evaluation, medical history will be taken, physical exam will be performed, and adverse events will be reviewed. Any lab tests, other evaluation, or referrals to evaluate the adverse event will be decided by the provider.

Study Schedule

	Screen	Day 0	Day 1	Day 7 (+1 day)	Day 10 (±1 day)	Day 28 (+2 days)	Monthly phone followup (1 year) (-/+7 days)
Informed consent	x	verify	verify	verify	verify	verify	verify
Review study inclusion/exclusion	x	x					
Medical history	x	x	x	x	x	x	x
Physical exam	x	x	As needed	As needed	As needed	As needed	
Injection site exam			x	x	x	x	
Vital Signs	x	x	x	x	x	x	
Urine pregnancy test (if applicable)		x					
Stool collection		x				x	
Blood draw	x	x	x	x	x	x	
Give Vaccine		x					
Record Adverse Events			x	x	x	x	x
Daily Symptom Diary through at least day 7		x	x	x	As needed	As needed	
Review of medications	x	x	x	x	x	x	x

- Some of the blood samples will be sent for specialized immunology testing at the Centers for Disease Control (CDC) and Tulane University. To protect your privacy, the data and samples will not be identified as belonging to you.
- Some of the collected samples/data will be stored for future research in order to better understand factors that contribute to vaccine response and human disease. Future research may include approved studies of genetic factors. To protect your privacy, these will be de-identified, meaning we will remove any data or information that would allow someone to identify you from the stored sample/data.

What Are The Risks and Discomforts Of The Study?

Injection of vaccine:

Possible local (surrounding the injection site) vaccine reactions include pain, tenderness, swelling, itching, rash, and redness at the injection site. In addition, local vaccine site reactions of skin color change (either darker or lighter) at and around the injection site is a risk. Up to 100% of volunteers are expected to have a local reaction. These reactions are expected to occur in the early days after the vaccine and resolve on their own. Changes in skin color have lasted as long as one year in up to 12% of people receiving mLT (related to dmLT) in earlier studies.

Based on known fIPV information, potential systemic reactions that resolve by themselves include fever (4%), fatigue (9%), poor appetite, and vomiting (<2%). The fIPV package insert data is given for infants, as the usual age of immunization is started after 6 weeks of age and

the frequency of side effects decreases with age. With dmLT, nausea, vomiting, poor appetite, diarrhea, and abdominal pain are possible risks, but in previous safety studies alone and with other vaccines, dmLT did not cause a significant difference in these events, so we estimate the risk to be low (<1%).

Because dmLT has not been previously administered with fIPV intradermally, the risks are unknown and we will monitor for any potential effects.

Headache, body rash, aches, and pains are other possible side effects of vaccines in general, although frequency of these risks are presumed too low to estimate and are not expected to be common for IPV or dmLT. Immediate hypersensitivity reactions including hives, anaphylaxis (severe allergic reaction), or other immune-mediated responses are possible, as with any vaccine.

You will be observed for 30 minutes after the vaccine in case of severe allergic reaction. If a severe reaction happens, you will be immediately treated by medical professionals and may require emergency room care if symptoms are serious.

You will be instructed to record any symptoms of not feeling well after the vaccine at home. If needed, you can call the study team to discuss your symptoms and decide if a medical visit is needed.

Blood draw: The total amount of blood to be drawn throughout the study is approximately 193.5 mL (13 tablespoons). Risks occasionally associated with blood draws include excessive bleeding, pain, bruising, or hematoma at the site of draw, lightheadedness, and syncope (rarely). Infection may occur rarely.

Topical Anesthetic Cream (use is optional): Risks occasionally associated with the use of topical anesthetic cream include temporary skin discoloration, skin irritation, rash, hives, and rarely, dizziness or drowsiness.

Other Risks:
You will be asked to defer routine immunization for live vaccines 28 days prior to the study or killed vaccines 14 days prior to receiving the study vaccine and until after 28 days after receiving the study vaccine. This may increase the risk that you will be infected with an influenza virus during this period (if in influenza season) or other vaccine-preventable disease.

As with any investigational vaccine, there is a possibility of risks about which we have no present knowledge. Subjects will be informed of any such risks should further information become available.

Guillian-Barre Syndrome (rapid-onset muscle weakness caused by the immune system damaging the peripheral nervous system) is a risk with vaccines though the risk is deemed low in this study and frequency of occurrence cannot be estimated as no causal relationship between the type of fIPV vaccine (IPOL) used in this study has been established. GBS has been temporally related to administration of another inactivated polio vaccine (not being used in this study).

Questions asked about pregnancy and birth control may make you feel uncomfortable. These questions will be asked in private and you do not have to answer any questions you do not feel comfortable answering.

Pregnant women may not participate in this study. If you are a female of child-bearing potential, a urine test will be done at the initial visit to make sure that you are not pregnant. There is a period of time during which this test may not be accurate, as you may be too early in your pregnancy to test positive. If you think you might be pregnant, you should not participate in this study. Because we do not know about risks of the study vaccine in pregnancy, females of child-bearing potential will agree to use effective contraception for the first 28 days of the study. Methods of contraception considered effective for this study are hormonal birth control, condoms with spermicide, diaphragm with spermicide, surgical sterilization, and intrauterine device.

Genetic Information Nondiscrimination Act (GINA)
Because stored specimens and data may be used for future approved research of genetic factors related to vaccine response or human disease, we would like to make you aware of the GINA law. A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA does not prohibit discrimination on the basis of an already manifest genetic disease or disorder.

What Are The Benefits of Participating In The Study?

- There is no benefit to you to participate in the study.
- There is benefit to society by helping with development of a potential new polio vaccine.

What Other Options Are There?
You may choose not to participate in the study.

Are There Any Costs?
There is no cost to you to participate in the study.

What Is the Compensation?
You will be compensated for scheduled in-person study visits that you complete. This is to compensate for some of your time lost to attend the visits. In some cases the income may be taxable.

- For the screening visit, $60 compensation is given after study enrollment. If you are not eligible or you choose not to participate in the study, you will not be compensated for the screening visit.
- $100 for scheduled study visit 1 on Day 0.(Alternates who do not receive vaccine on Day 0 also receive the $100 compensation).
- $70 per visit for scheduled study visits 2-5 (4 total)

Compensation will be distributed according to the following schedule for those who complete all study visits (compensation will be prorated if any visits are missed):

- $230 on Day 7
- $210 on Day 28

Can You Withdraw or Be Withdrawn From This Study?

You may discontinue your participation in this study at any time. If you decide to stop participating in the study, you will be invited to provide information about adverse events for the safety portion of the study if you do not wish to have sample collection. However, you may choose to discontinue participation in the study entirely. There are no consequences if you choose to stop participating in the study. The researchers also may discontinue your participation in the study at any time.

What About Confidentiality of Your Health Information?

What health information will be used and disclosed for this study?
The health information we plan to collect for this study is listed below.

- Medical history and examinations
- List of medications you are taking
- Labs obtained for the study: urine pregnancy test (if applicable); blood work and stool studies to study immune system response to study vaccine (anti-LT antibodies ELISA, gut homing (α4β7) antibody secreting cells by ELISPOT, polio serum neutralizing antibodies, baseline gene transcription transcriptomics), fecal neutralizing antibodies and fecal IgA assays)
- Childhood vaccine record
- Information that identifies you, such as your name, address, age, and sex
- Reports from hospital and clinic visits, labs and other test results will only be obtained in the event that clarification of your medical history is needed or if there is an adverse event.

Who is disclosing your health information for this research study?

- The University of Vermont Medical Center
- Other doctors' offices and hospitals where you may receive medical care while this study is active.
- Will use record release form for records from outside institutions

Who will use your health information in this study?
Our research team will use your health information. We may also share it with those who assist with the conduct of the research or oversight of the activities for this study. The representatives from the institutions, organizations, and agencies are listed below.

- The University of Vermont and its Committees on Human Research

- Officials from agencies and organizations that provide accreditation and oversight of research
- Safety Monitor
- The University of Vermont Medical Center
- Other researchers and centers that are a part of this study, including individuals who oversee research at those sites (some labs will be performed at the Centers for Disease Control (CDC) and some at Tulane University)
- Company(ies) that provide drugs for this research project
- Federal and state agencies that oversee or review research information, such as the U.S. Food and Drug Administration (FDA)
- Your health insurer, for any related care that is considered billable

Your health information is protected by a federal law called the Health Information Portability and Accountability Act (HIPAA). Once your health information is shared outside of the University of Vermont Medical Center, we cannot guarantee that these laws will continue to apply. As a result, your health information could be further disclosed for other purposes. In the absence of a Certificate of Confidentiality, it is also possible for a court or other government official to order the release of study data. The confidentiality of your health information cannot be guaranteed if you agree it may be used in this study.

How long will your health information be used for research?
Your permission to use your health information will not end until the study is completed. During this study, you will not have access to study data. You may ask for your data once study activities are complete. You have a right to receive a copy of the information in your medical record at any time.

What if you decide not to give permission for research use of your health information?
If you decide not to allow the use and disclosure of your health information, you may not take part in this study. Your decision will have no effect on your current or future medical care.

If you choose to stop taking part in this study in the future, you may cancel permission for the use of your health information. You should let the research team know that you are cancelling your permission. A member of the research team will assist you in making your decision effective. The study will continue to use the health information already collected for the study before you cancelled your permission, and you cannot get back information that was already shared with others.

Who can answer your questions about the use and disclosure of your health information?
If you have questions or concerns about the use and disclosure of your health information, you should ask a member of the study team at the Vaccine Testing Center 802-656-0013 or the Privacy Officer at The University of Vermont Medical Center, Inc, at (802) 847-2667.

Safeguarding Your Health Information

A record of your progress will be kept in a confidential form in a locked research office at the Vaccine Testing Center. The security of your record will be maintained by the research team. The results of this study may eventually be published and information may be exchanged between medical investigators, but patient confidentiality will be maintained.

If your record is used or disseminated for government purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

The results of the study may be published, whether it is shown that the test vaccine works or not. You will never be identified in any publications. You will be able to get a copy of the published results from the study team.

You may be requested to provide your name, social security number, and address. This information will be disclosed one time to either the University of Vermont's Procurement Services Department or UVM Medical Center Accounts Payable Department for purposes of reimbursing you for participation in this study. If you are not a US Citizen or Permanent Resident Alien you will be required to complete additional paperwork for payment.

Clinical Trials Registration

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

What Happens If You Are Injured?

If you are injured or become ill as a result of being in this research, The UVM Medical Center, the hospital partner of the University of Vermont, will provide reasonable and usual medical care for that injury or illness. There will be no cost to you if the conditions listed below apply to your injury or illness. These conditions are:

1. The investigator determines that your injury or illness results from the research and not from your underlying condition or its usual treatment.
2. You let the investigator know about the injury or illness when you first notice it; and
3. You follow medical advice about proper treatment options for the injury or illness.

If the above conditions are not met, the UVM Medical Center may claim payments for your medical treatment from the study sponsor or your insurance company when these payments are allowed. ***If we bill your insurance for this care, you will be responsible for any associated co-payments or deductibles.***

For an injury or illness that results from being in this study, the University of Vermont and The UVM Medical Center will not offer you any other payments, such as lost wages or expenses, except for your medical care. Even though you may receive medical care at no cost to you under certain conditions if you are in this study, the UVM Medical Center and the University of Vermont do not admit to any responsibility for an injury or illness that results from being in the study.

If you agree to take part in this study and you sign this consent form, you are not giving up any of your legal rights.

Contact Information

You may contact Dr. Cowan the Investigator in charge of this study, at 802-847-8600 for more information about this study. If you have any questions about your rights as a participant in a research project or for more information on how to proceed should you believe that you have been injured as a result of your participation in this study you should contact the Director of the Research Protections Office at the University of Vermont at 802-656-5040.

Statement of Consent

You have been given and have read or have had read to you a summary of this research study. Should you have any further questions about the research, you may contact the person conducting the study at the address and telephone number given below. Your participation is voluntary and you may refuse to participate or withdraw at any time without penalty or prejudice to your present and/or future care.

You agree to participate in this study and you understand that you will receive a signed copy of this form.

_____ _____

Signature of Subject Date

_____

Name of Subject Printed

_____

Signature of Principal Investigator or Designee Date

_____

Name of Principal Investigator or Designee Printed

Name of Principal Investigator: Kelly Cowan, MD
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Telephone Number: 802-847-8600