CLINICALINVESTIGATIONPLAN(CIP) TITLE: Mesh Suture

PRINCIPAL INVESTIGATOR:

Dr. Garen Koloyan

Wigmore Clinic, 56 Pushkin Street, 0002 Yerevan, Armenia

30 June 2018; Revised 19 April 2019

OBJECTIVES

Determine whether Mesh Suture achieves an acceptable safety and efficacy profile with the appropriate performance for internal load bearing closures, and with acceptable risks and benefits.

BACKGROUND

Sutures are flexible linear elements that appose tissues and are "self-holding" with a surgically created knot. When tissues are under tension, such as the closure of an abdominal wall after laparotomy, the sutures cut through the tissues in what is known as "suture pull-through" and create incisional hernias. The hernia rate after primary laparotomy depends on the patient population, but is over 10%. In some high-risk populations, even with a small 3 cm laparoscopy incision, the hernia rate is over 30%. In primary hernia repair, use of sutures alone yields a 60% hernia recurrence rate at 10 years. Mesh has become commonplace in order to decrease incisional hernia recurrence rates in primary hernia repairs.

A novel mesh suture, designed at Northwestern University (Chicago, IL) by Dr. Gregory Dumanian, has shown improved outcomes in pre-clinical animal models and these results are included at the end of this document. Dr. Dumanian has employed the concept of using a mesh-like suture already in his clinical practice. He has cut strips from an FDA-approved piece of hernia mesh, and used them as sutures, tying them with knots.

Based on improved outcomes in pre-clinical and analogous clinical data in comparison to standard suture, Dr. Dumanian now proposes the use of a medical grade mesh suture of his design and fabrication in the treatment of orthopedic conditions. These are internal permanent sutures and will not be removed. They are made of the identical material (polypropylene) used in standard sutures. In fact, the mesh sutures are 12-14 standard surgical sutures that are braided to create a single mesh suture. Dr. Dumanian had a meeting with the FDA (see attached File A) in December 2016. At that meeting, it was decided that the Mesh Suture did not represent a significant added risk over that of standard suture, and therefore would be able to follow a 510(k) pathway without a clinical trial. However, in order to gain clinical data before official product launch, we propose this clinical trial.

STUDY TIMELINES

It will take approximately 12 months to accrue 80 patients into the study. The patients will be followed 1 year after the implantation of the mesh suture. It will take approximately 3 months to collect the data after the final patient has had their one-year final examination.

STUDY ENDPOINTS

30 days and 12 months

PRIMARY OUTCOMES

1. Surgical site occurrence (SSO) within 30 days

Superficial infection

Deep infection

Dehiscence

Hematoma

Necrosis

Non-healing wound

Seroma

2. Delayed infection or sinus within 1-12 months

Office removal of suture or knot

Return to the operating room (OR) for draining wound

Knot removal for palpability (added April 20, 2019)

SECONDARY OUTCOMES

1. Operating room handling of suture

- Surgeon satisfaction with suture for repair of tissues (min 1, max 5)
- Intraoperative suture breaking or fraying (min 1, max 5)
- Quality of knot (min 1, max 5)
- Needle size and shape appropriate (min 1, max 5)

2. Rehospitalization for any wound issue within 30 days

3. Return to the OR for any reason within 1-12 months

4. General rating of the suture by surgeon

Excellent

Good

Fair

Poor

INCLUSION CRITERIA

Consecutive patients undergoing planned surgery at the Wigmore Clinic and Arabkir Joint Medical Center in Yerevan, Armenia, and requiring deep soft tissue approximation and/or ligation:

1. Age: more than 1 year
2. Gender: male or female
3. Indications for use: tendon lengthening, ligamentoplasty, tendon repair, repair of joint capsules, other deep tissue approximations

EXCLUSION CRITERIA

1. No planned need for closure of deep soft tissues
2. Pregnancy
3. Age less than 1 year
4. Repair of skin or other tissues with epithelium

Indications for Use	The Mesh Suture is indicated for use in soft tissue approximation and/or ligation. Not to be used for the skin.
Patient Population	Subjects will be recruited from a population of patients treated for orthopedic conditions by Dr. Garen Koloyan
Study Size and Center	N=80 patients at Wigmore Clinic Arabkir Joint Medical Center in Yerevan, Armenia
Clinical Study Design	Safety and efficacy trial of a medical device (surgical suture). Prospective, Non-blinded and non-randomized, Multi-center, Single-surgeon
Primary Safety Endpoints	Surgical site occurrence (SSO) with 30 postoperative days Delayed infection or sinus within 1-12 months
Secondary Effectiveness Endpoints	Operating room handling Rehospitalization for any wound issue within 30 days Return to the OR for any reason within 1-12 months General rating of the suture by surgeon
Study Flow	SCREENING 1. Preoperative assessment by the surgeon to confirm that the patient meets the study entry criteria. 2. Informed consent obtained from patient by study staff. SURGERY 1. Perform surgery and close deep tissues with Mesh Suture 2. Record intraoperative information on CRF. PATIENTS EXCLUDED FROM FURTHER FOLLOW-UP Based on the tissues, patient's condition, and all other intraoperative factors, Dr. Koloyan may decide not to use a mesh suture. These patients will not undergo any further follow-up nor be included in the safety and effectiveness analyses. INITIAL FOLLOW-UP Patient follow-up will be per Dr. Koloyan's established protocols. All patients will be seen at least or contacted by study staff by 30 days to assess healing of the incision and assess for possible SSO. FINAL FOLLOW-UP Late patient follow-up will be per Dr. Koloyan's established protocols. All patients will be seen at least or contacted by study staff by the end of the study period (12 months after the surgery) to assess healing of the incision, functional outcome of surgery, and assess for possible delayed infection.
Data Analysis	Clinical Events Committee (CEC) will meet as necessary to review patient outcomes and complications. It will comprise of the PI (Dr. Garen Koloyan), Dr Vartges Avagian, independent urologist in Yerevan, and the Sponsor's Representative (Dr. Gregory Dumanian).

PATIENT SELECTION

Will be at the discretion of the PI, with patients matching inclusion criteria and not have any exclusion criteria. The patient should be able to have postoperative follow-up visits and have the appropriate guardians to provide consent if under the age of 18.

SAFETY AND EFFECTIVENESS

This safety and effectiveness study is intended to demonstrate that overall patient outcomes are no worse than or adversely different from the current surgical standard of care. In addition to overall patient outcomes, the study will also examine adverse outcomes related to the use of the suture.

An overarching issue is that the suture used in the procedure reflects only a small part of the total treatment of the patient – including what adverse occurrences are responsible for surgical morbidity and mortality. Robust evaluation of suture closures is best assessed in the setting of an animal study where the surgical wound can be opened and tested at the end of the follow-up period. This then allows the investigator to readily inspect the suture line and assess the abdominal suture closure for safety and effectiveness endpoints including suture pull-through. This is not possible in the treatment of humans. Therefore, safety is best noted by the achievement of standard wound healing rates and the absence of delayed infections in comparison to historical controls. Efficacy is best noted by the achievement of standard functional outcomes in comparison to historical controls.

DESCRIPTION AND ANALYSIS OF ALL INCREASED RISKS TO THE RESEARCH SUBJECTS

1. All of these subjects will be undergoing orthopedic surgery, and there are established baseline rates of SSO for these procedures. Each hospital will have its own rate of SSO based on the procedures performed and the population of that facility. While all procedures are associated with risks and SSO, it is not expected that there will be significant ADDED risk to the patient using a mesh suture for a deep internal closure. In fact, animal data implies that using a mesh suture will result in a stronger earlier repair.
2. Patients undergoing surgery have other risks of medical complications. It is NOT expected that there will be additive medical risks of closing with mesh suture.
3. Mesh suture is made of a material commonly used for sutures (polypropylene), without any added chemicals. It is treated with heat and pressure – two items that are also used commercially in the fabrication of hernia meshes. The mesh suture has passed all of the necessary FDA tests for biocompatibility and the absence of toxins.
4. The surgeon does not need to alter their technique in any way.
5. It is expected that a mesh suture closure will take the same amount of time as closures with standard sutures.
6. Mesh Suture meets all of the criteria as other sutures for strength and the quality of the needle attachment. It is physically larger than other sutures, but achieves a small knot with the collapsing of the filaments.
7. The protocol allows the use of this suture in a vulnerable population, namely children under the age of 18. Polypropylene sutures have been used extensively in vascular and heart surgery in children as well as in other soft tissue procedures with an excellent record for biocompatibility. Therefore, use of mesh suture in this age group does not represent a significant added risk.

Examples from the literature are below of using polypropylene sutures and meshes in children:

a. Perez-Negueruela C, Carretero J, Mayol J, Caffarena JM. Surgical closure of multiple large apical ventricular septal defects: how we do it. *Cardiol Young.* 2017;27(3):588-591.

b. Baradaran N, Wood CM, McCoy OO, Prasad MM, Stec AA. Laparoscopic intra-abdominal patent processus vaginalis ligation in pediatric urology practice. *J Pediatr Urol.* 2017;13(5):512.e1-512.e6.

c. Ordorica-Flores R, Figueroa-Portillo R, Pérez-Escamirosa F et al. Pediatric inguinal hernia repair with a single-incision approach using an Endo Close™ suturing device. *Surg Endosc.* 2016;30(11):5134-5135.

d. An G, Zhang H, Zheng S, Wang W, Wu Q, Xing Q. Minimally invasive surgical closure for doubly committed subarterial ventricular septal defects through a right subaxillary thoracotomy. *Interact Cardiovasc Thorac Surg.* 2016;23(6):924-928.

e. Eltayeb AA, Ibrahim IA, Mohamed MB. The use of PROCEED mesh in ventral hernias: a pilot study on 22 cases. *Afr J Paediatr Surg.* 2013;10(3):217-221.

DATA AND SPECIMEN BANKING

There will be no specimens stored or banked.

Data will be secured on the password-protected laptop, with paper backups located in a locked file cabinet by Dr. Koloyan. Paper consents will be similarly located in a locked file cabinet.

Dr. Dumanian's participation in the Clinical Study will be limited to the following activities:

Data analysis

Submission of results

Ad hoc advisory to study investigators as a CEC member.

Dr. Dumanian will not be performing any of the surgeries in the study.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

A data monitoring committee (DMC) will be established by the sponsor to review outcomes for these patients, and the committee will then categorize all complications as to relatedness to the use of surgical suture. This data will be reported every other month to the IRB and the sponsor.

The DMC will include at least 3 members: two independent monitors – Dr. Jonah Stulberg and Dr. Samir Attar (Northwestern Feinberg School of Medicine, Chicago, IL, USA), a study manager – Dr. Davit Abrahamyan (Arabkir Joint Medical Center, Yerevan, Armenia) and when necessary a statistician will be arranged from the Deparment of Social Medicine, Feinberg School of Medicine. Drs. Stulberg and Attar have no financial interest in the company, Dr. Stulber is in preparation to perform an FDA approved Mesh Suture trial at Northwestern Memorial Hospital (Chicago, IL, USA).

A moratorium on the use of the suture will be put in place if three (3) early surgical dehiscences of deep tissues occur, or an SSO rate of 15%. All complications and/or deaths will be reviewed for possible connection to the suture used for closure. Upon any death attributed to the means of suture closure, there will be a moratorium on this study. The data monitoring committee will analyze these serious complications, and give a report to the IRB and the sponsor if the study as to the cause of these serious complications, and if the trial should continue. The data will be reported every other month to the DMC via email. All adverse events will be communicated in written form as outlined below. Serious adverse events will be communicated both electronically and by written letter. The sponsor will receive this document, and the committee will place a moratorium on further cases for the complication rates described above. The DMC will report to the IEC after [successful] resolution of issues based on

correctable factors including changes to the CIP and patient selection.

Emergency ad-hoc meetings of the DMC will be held upon request by any of the 3 members of the committee via Skype. The meetings will be documented by Dr. Stulberg, and a report delivered to the sponsor.

WITHDRAWAL OF PARTICIPANTS

Patients can choose to withdraw from the study at any time. As the Mesh Suture will already be implanted, there is no mechanism for removal of the suture other than a repeat surgery, and this will only be performed based on clinical indications.

CLOSURE OF THE STUDY

For this first-in-human use of mesh suture, 80 cases will be performed in this safety and effectiveness study. The hypothesis is that the mesh suture will be equivalent in performance to standard suture. The study will be closed upon accrual of 80 patients, final follow-up of these patients. An early moratorium of the study will occur with a 15% rate of SSO, or 3 early and unexpected dehiscenses of deep tissue closure attributable to the suture as judged by the data monitoring committee. Early closure of the study will occur based on the judgement of the PI, the sponsor, and an early demonstration of equivalence to the results of standard suture as judged by a lack of early and late infections and appropriate postoperative surgical results demonstrating appropriate tissue approximation for internal load-bearing closures.

INFORMATION ON MESH SUTURE

Like all sutures, DURAMESH apposes soft tissue. The device pierces the tissue with the aid of a standard needle, and the flexible cylindrical mesh body consisting of braided filaments achieves tissue apposition by means of a surgically created knot. The open body macroporous design permits tissue ingrowth into and around the braided filaments.

BASIC FEATURE DESIGNS

A needle is swaged to the mesh body to facilitate passage through tissue. It has a linear and flexible design. The cylinder flattens with radially applied force. It approximates tissue with the creation of a self-holding knot. It allows for tissue ingrowth around the filaments. The mesh body consists of individual filaments that are braided and bonded with heat and pressure. It is constructed with polypropylene filaments that distribute forces through their shape, size, and the number of filaments. Linear filaments exist to maintain porosity. The filaments collapse at the knot to create a smaller knot profile. The mesh bodies are attached to standard surgical needle sizes.

Filament size is an important characteristic for biocompatibility. As has been recently shown in independent laboratory studies, the foreign body reaction to small filaments is qualitatively different than the foreign body reaction of a larger diameter filament made of the same material.1 This improved biocompatibility for smaller filaments was recently discussed in a peer reviewed and accepted

manuscript by Dr. Dumanian.

There are four sizes of DURAMESH: 2-0, 0, Number 1, and Number 2, and each is composed of a hollow cylindrical braided weave of standard polypropylene filaments. The DURAMESH 2-0 is composed of 12 polypropylene filaments (twelve 100-micron filaments), the DURAMESH 0 is composed of 12 polypropylene filaments (four 150-micron filaments and eight 100-micron filaments), DURAMESH Number 1 is composed of 18 polypropylene filaments (eighteen 100-micron filaments), and DURAMESH Number 2 is composed of 18 standard polypropylene filaments (six 150-micron filaments, and twelve 100-micron filaments).
The polypropylene filaments are braided around a mandrel and then treated with heat and pressure to create bonds. There are no additional chemicals or treatments used in the manufacturing.
After braiding, the leading edge of the mesh body is attached to a conventional needle via a mechanical swaging process. The curved needle is manufactured from medical grade stainless steel 470SS that complies with ASTM standard F899.

Mesh Suture is available in USP size equivalents 2-0, 0, Number 1, and Number 2 and will be supplied in pre-cut 36-inch lengths.

DIRECTIONS FOR USE

Surgeons should select DURAMESH for indications of internal approximation and/or ligation of soft tissues, where there is a potential for suture pull-through or tearing of tissues. Selection of a particular DURAMESH suture with a particular needle will depend on the quality of the tissues and the specifics of the surgical procedure. The surgeon will rely on his or her years of training, education, and experience for DURAMESH size selection. The surgeon will also be guided by the USP designation, namely that a 2-0 DURAMESH will be selected as a substitute for a 2-0 standard suture, and similarly for the 0, Number 1 and Number 2 DURAMESH sizes.

BIOCOMPATIBIITY

Based on the FDA guidance for Biocompatibility “Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process”, the device is categorized as an implant, tissue /bone contact, long term ‘C’ duration. DURAMESH is manufactured from the same polypropylene material as the predicate device ‘Sharpoint polypropylene suture’ and is manufactured by the same supplier, Surgical Specialties Corp.
Biocompatibility testing was performed as per International Standard ISO 10993-1 by
the NAMSA Corporation (Northwood, OH) including cytotoxicity, sensitization, irritation or intracutaneous reactivity, chemical characterization, acute systemic toxicity, material-mediated pyrogenicity, genotoxicity, implantation/histology, endotoxin testing, and pyrogen testing. All applicable FDA standards were passed for these tests. Carcinogenicity, chronic toxicity, and subchronic toxicity are addressed in a "Risk Analysis" by the NAMSA corporation The needles used for DURAMESH are made from 470-grade stainless steel surgical wire.

POTENTIAL RISKS TO PARTICIPANTS

The Mesh Suture will be manufactured (fabrication, sterilization and packaging) using GMP standards by one of the largest suture companies in the world, Surgical Specialties. The risk of contamination or inadequate preparation is very low considering the experience of the manufacturer. This will minimize the risk of an issue with the suture itself (sterility, composition, tensile characteristics, etc.) to the patient.

The overwhelming majority of risks to the patient is inherent to surgery and the surgical process, and is not relatable or attributable to the suture used for closure. The risks of surgery as delineated in this submission far outweigh any ADDED risks of using Mesh Suture for closure as opposed to standard suture. There are risks of the use of a permanent suture in terms of delayed infection.

POTENTIAL BENEFITS TO PARTICIPANTS

Pre-clinical testing in 14 human-sized pigs shows a stronger and earlier hold of tissues of using Mesh Suture in comparison to standard sutures. While these are potential benefits, the actual benefits and risks to the patients are unknown.

Analogous "mesh sutured repairs" in 500 humans have been performed for over 3 years at Northwestern Memorial Hospital, Walter Reed, Ohio State, Brown University, Memorial Sloane Kettering, as well as other American hospitals without any unexpected outcomes different than that expected for standard suture. The results of these patients treated have been presented locally, nationally, and internationally to large audiences of surgeons without any voiced concerns.

VULNERABLE POPULATIONS

See above. Polypropylene is a well-established suture material and is well-documented in the use in children as having an excellent safety profile. Therefore, its use in this study protocol is acceptable. It will not be used in pregnant women and in infants under 1 year.

COMMUNITY-BASED PARTICIPATORY RESEARCH

Not applicable.

SHARING OF RESULTS WITH PARTICIPANTS

Will be performed one (1) year after surgery as requested by the patient.

SETTING

The study will occur at the Wigmore Clinic and Arabkir Joint Medical Center in Yerevan, Armenia.

RESOURCES AVAILABLE

Dr. Koloyan is an established orthopedic surgeon and has the necessary time and expertise to perform this clinical trial, aided by his staff.

PRIOR APPROVALS

None

RECRUITMENT METHODS

Recruitment will be through the clinic of Dr. Koloyan.

NUMBER OF LOCAL PARTICIPANTS

It is anticipated that up to 100 patients will need to be consented preoperatively to have 80 patients who will have the potential to have an internal mesh suture closure.

CONFIDENTIALITY

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:

The issues of patient privacy will be identified in the consent form.

OBSERVATION AND RECORDING OF RESULTS

Will be performed by the PI and his designees based on the routing performance of clinical practice. Superficial infection will be defined as the use of oral antibiotics for erythema that is more consistent with a bacterial process than with other explanations including pressure induced erythema, allergic reactions of the skin, or irritation from skin sutures. A deep infection is defined as purulent drainage from the wound requiring an opening of the skin by the surgeon, a return to the operating room for drainage or wounds, and/or cultures from internal structures consistent with an infection. Hematoma is defined as a collection of blood as the primary cause of a lack of appropriate wound healing, and a hematoma with secondary infection of the clot is also defined as a hematoma. A seroma is defined as clear fluid found underneath an intact incision or draining through a wound as the primary cause of a lack of appropriate wound healing. A delayed sinus is defined as a area of a previously healed incision that leads to the Duramesh knot or filament that does not resolve with antibiotics, or requires an opening of the wound and Duramesh removal for resolution.

ADVERSE EVENTS

The documentation and reporting of all adverse events as per ISO/DIS 14155:2018(E) has been agreed to by the PI and sponsor and a signed document to this effect was created on June 20, 2018. For the protection and benefit of patients, it is agreed that Dr. Koloyan will regularly communicate with the EIC. All adverse events will be categorized according to ISO/DIS 14155: 2018 guidelines. Any question regarding categorization will be reviewed by the data monitoring committee, made up of the members of the Wigmore Clinic IEC and chaired by Dr. Davit Abrahamyan, as well as outside reviewer Dr. Jonah Stulberg, Assistant Professor of Surgery at Northwestern Feinberg School of Medicine.

COMPENSATION FOR RESEARCH-RELATED INJURY

The use of a suture for closure of deep internal tissues is within the standard of care, and there are risks of infection, need for repeat surgery, wounds, and delayed infection as there are with any surgical suture. It is not thought that closure with a Mesh Suture will significantly change those risks. Therefore, there will be no compensation for research related injury. However, in the case of postoperative complications related to the Mesh Suture within the course of the study (1 year after the surgery with Mesh Suture), Dr. Koloyan will perform the revision surgery free of charge.

ADDED ECONOMIC BURDEN TO PARTICIPANTS

None. There are costs of surgery and postoperative follow-up that are unchanged with either using or not using the Mesh Suture.

CONSENT PROCESS

The consent will be obtained by the attending surgeon, or by the study coordinator. This will occur preferably in the clinical office of the attending, but also in the preoperative holding area before surgery. We expect the consent process to take 10 minutes. Suture examples will be shown to the

patient. Steps taken to minimize coercion or influence will be contained in the consent form. Consent will be obtained by native Armenian speakers.

All patients who meet inclusion criteria and who do not have exclusion criteria will be approached for consent, so long as their legal guardian or legal representative is present and consents to the orthopedic procedure.

PROCESS TO DOCUMENT CONSENT IN WRITING

The process to document consent and re-consent in writing will be done as follows, per GCP guidelines: the consent form will be signed and personally dated by the participant and/or the legal representative/guardian and by the person who conducted the consent prior to any study procedures. A signed copy of the consent form will be given to the participant or the legal representative. This process will be documented in the subject source documents.

DRUGS OR DEVICES

Three different sizes of Mesh Suture, namely 2-0, 0 and Number 2, will be under the control of the study coordinator, and will be disbursed in the operating room at the time of the procedure. The study coordinator will fill out the necessary patient data form at that time. For traceability, lot number and expiration date for finished and packaged suture will be recorded. The sutures will be locked in a cabinet in the operating room with keys controlled by Drs. Koloyan and Abrahamian. They are labelled "For investigational use only".

STUDY PARTICIPANTS

Dr. Garen Koloyan is head of the Wigmore Clinic and the PI for the study. He completed medical school at the Tver State Medical University in Russia, where he received a medical degree. He completed his training in Traumatology and Orthopedics, and did fellowships both in Toronto at the Hospital for Sick ChidIdren and the Shriner's Hospital for Crippled Children in Portland Oregon. He followed this with being Staff physician at the Insitution of Traumatology and Orthopedics in Yerevan, followed by a position as Chief of Pediatric Orthopedic Surgery at the same institution. From 2007 until now, he was head of pediatric trauma and orthopedics at the "Arabkir" Joint Medical Center in Yerevan. In 2017, he became the head of the Pediatric Orthopedic Service at the Wigmore Clinic in Yerevan. He has over 89 published articles, abstracts, and publications.

Dr. Gregory Dumanian is the sponsor of the project and is the Science Officer for the Mesh Suture Co. He is also the Chief of Plastic Surgery at the Northwestern Memorial Hospital. He studied medicine at the University of Chicago, and graduated in 1987. He studied surgery at the Massachusetts General Hospital, plastic surgery at the University of Pittsburgh, and hand surgery at the Curtis Hand Center. He has over 140 publications, and has served as visiting professor over 20 times to various universities both nationally and internationally. He submitted his patent for a mesh suture in 2012.

The Wigmore Clinic

Wigmore Clinic is a modern medical center, which offers wide range of inpatient and outpatient services in orthopedics, sport medicine, spine surgery, vascular surgery, pediatrics, dentistry and interventional radiology. The Clinic was founded in 2017. The clinic's facility is designed specifically to provide maximum comfortability and highest possible standards of care. Wigmore is a dynamic and rapidly growing medical center that has a commitment to evidence based clinical practice. Being affiliated with Yerevan State Medical University the clinic is involved in education and academic research. The clinic has a mission to build a culture of effective teamwork and quality: ensuring safe and patient focused care across all departments of the organization. Wigmore Clinic's values are: commitment to continual improvement, high moral and professional standards, trust, respect and transparency.

The advantage of Wigmore Clinic is the coordinated care in teams of experts, who are working to achieve the best results in treatment. Most of the leading surgeons of the hospital were trained in USA and Europe and created the wide network with medical specialists from these countries, who support the clinic in continual education and management of the most complicated cases.

Arabkir Medical Center

"Arabkir" Joint Medical Center – Institute of Child and Adolescent Health (Arabkir JMC) is the largest pediatric hospital in Armenia, which realizes large-scale medical activities. The center provides medical services, including prevention, diagnostics and treatment of different child diseases, follow-up services for children with chronic urological and surgical, gastroenterological problems as well as with bronchial asthma, epilepsy, diabetes and hepatology, orthopedics, nephrology, endocrinology-related diseases, psycho-social and rehabilitation services.

"Arabkir" JMC also provides services for emergency cases and a number of services for adults in the fields of urology and general surgery, nephrology and kidney transplantation, laboratory diagnostics. As a multidisciplinary medical structure, Arabkir JMC provides medical assistance and care to thousands of children every year. The Service of Trauma and Orthopedics (STO) has a long history of providing high quality care to patients with musculoskeletal disorders. It is one of the leading departments not only in Armenia, but in the region. Many patients from neighbor countries such as Georgia, Russia, Ukraine, and Iran come to this Service for surgical treatment and rehabilitation. The hospital has several Child Development and Rehabilitation Centers function in different regions of Armenia.

TRACEABILITY

Lot number, reference number, and date of expiration will be recorded for each case. In the event of need for follow-up of patients depending on information from the sponsor, it will be the responsibility of the PI to reach out and communicate with the patients in terms of need for follow-up, increased monitoring, and even surgery for addressing of the issue.

LIABILITY

As is the custom for clinics and surgeons in Armenia, neither the Wigmore Clinic nor Dr. Koloyan carry malpractice insurance.

MISSING DATA

It is the responsibility of the PI to accurately and completely fill out the CRF. Missing data will be analyzed by the data monitoring committee and completed with assistance of the PI. Follow-up either in person at the Wigmore Clinic or by telephone is the responsibility of the PI.

DATA FROM THE MEDICAL RECORD

All patients in this study will grant approval for the appropriate aspects of their medical record (including the operative report, photographic documentation, x-rays, laboratory findings, culture reports, and other pertinent information to be included in the Clinical Evaluation Trial. Organizations

that may inspect and copy the medical chart include the IRB and other representatives of this institution, government agencies such as the US Food and Drug Administration (FDA) and other regulatory authorities in other countries including the European Union; and the study sponsor Mesh Suture Inc. The sponsor, monitors, auditors, the US Office for Human Research Protections (OHRP), the US FDA, as well as other government organizations may be granted direct access to the medical record to conduct and oversee the research.

DEVIATIONS FROM PROTOCOL

Any deviation from the protocol judged minor will be documented by the PI and judged whether the patient and outcome will be included in the final report. Any deviation from the protocol judged major including will be communicated immediately with the data monitoring committee for resolution.

FINAL REPORT

A final report of data will be provided by the PI to the sponsor. This will include an evaluation of all primary and secondary endpoints. Efforts will be made to obtain long term follow up either by office visits at the Wigmore Clinic, and/or telephonic interviews of subjects. Duramesh will be analyzed in terms of the size used, the location placed (tendon, joint capsule), running or interrupted closure, surgeon satisfaction, and a qualitative report of issues of use of the suture. The appropriate statistical tests including t-tests for the comparison of groups will be employed for data analysis.

1. LITERATURE REVIEW OF PRE-CLINICAL TESTING

1.1. Pre-clinical Rat *In-Vivo* Hernia Model using Mesh Suture Prototype[2]

1.1.1. Objective

Demonstrate in an established rat hernia model a novel mesh suture prototype would have decreased pull-through in comparison to standard suture.

1.1.2. Methods

Incisional hernias were produced in N=30 rats according to an established hernia model. The rat hernias were randomized to repair with either two 5-0 polypropylene sutures or two mid-weight polypropylene mesh sutures. Standardized photographs were taken prior to repair and 1 month after repair.

Edge-detection software was used to define the border of the hernia defect and calculate the defect area. Histology was performed on all mesh suture specimens, with in-growth graded according to the ASTM 4-point scale.

1.1.3. Results

Table 1: Results from Rat Study

Study Endpoint	Mesh Suture Prototype	Conventional Suture
Randomization Assignment, N	17	13
Pulled-Through, n (%)	0 / 34 (0)	17 / 26 (65)
Mean Area of Recurrent Defects Following Repair, mm^2	178	267
Change in Defect Area, %	**57.4% Reduction**	**10.1% Increase**
ASTM 4-Point Scale	Excellent (ASTM3) fibro-collagenous in-growth in 13/17 specimens	Good (ASTM2) in-growth in 4/13 suture specimens

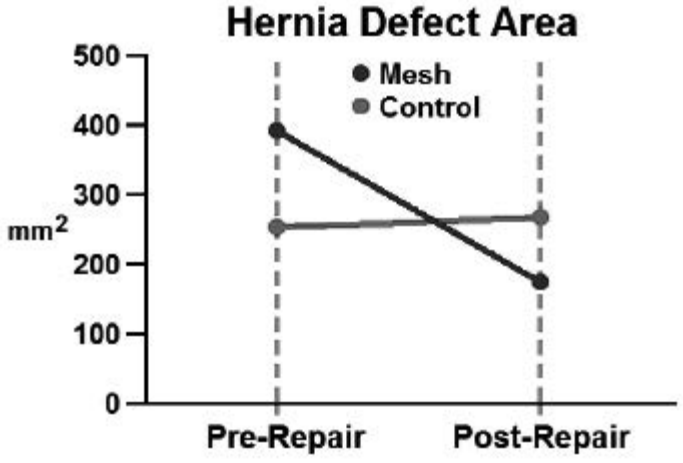


Figure 1: Rat hernia repair data

[2] Souza JM, Dumanian ZP, Gurjala AN, **Dumanian GA**. In vivo evaluation of a novel mesh suture design for abdominal wall closure. *Plast Reconstr Surg.* 2015;135: 322e.

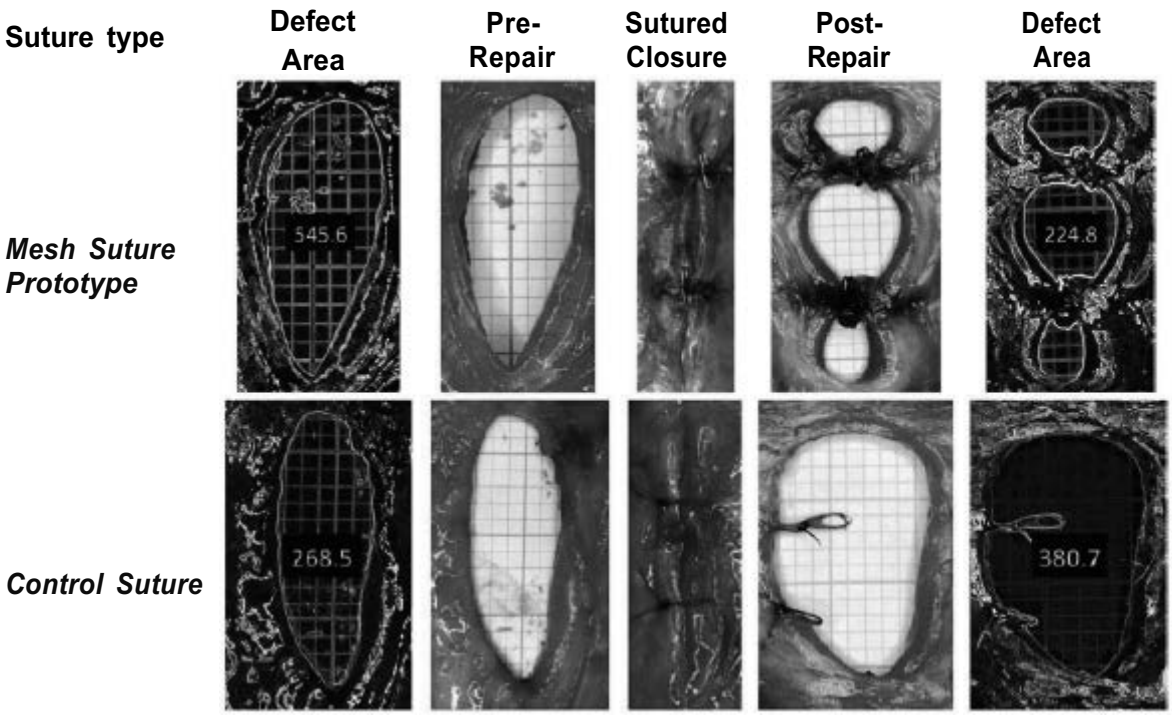


Figure 2: Rat hernia repair images

1.1.4. Conclusion

The **Mesh Suture had improved resistance to device pull-through** compared to conventional polypropylene sutures in this 30-day rat hernia model. The design elements of Mesh Suture may prevent early hernia repair failure by more evenly distributing distracting forces at the device-tissue interface. Tissue incorporation of the device itself was documented and may play a role in decreased pull-through.

1.2. Pre-clinical Porcine *In Vivo* Animal Study using a Mesh Suture Prototype[3]

1.2.1. Objective

Characterize Ultimate Tensile Strength (UTS) of porcine abdominal wall closures at 8 days using a 1.7 mm Mesh Suture in comparison to standard suture.

1.2.2. Summary

This study was published in the British Journal of Surgery and utilized 93 kg pigs in a clinically relevant and realistic laparotomy closure model. A 1.7 mm Mesh Suture prototype was compared to 0-polypropylene for strength of closure at 8 days after implantation.

1.2.3. Background

Laparotomy closure failure leads to incisional hernia formation in up to 23% of patients requiring the risk, expense, and discomfort of a second surgery.

1.2.4. Methods

In Vitro – A 1.7 mm Mesh Suture and a 0-polypropylene suture were tested for resistance to pull-through in ballistics gel.

In Vivo – Closure of midline laparotomy segments was performed, alternating between 2 mm Mesh Suture prototype and 0-polypropylene in N=12 female swine.

Tissue segments were subsequently subjected to mechanical testing at 8 days in N=10 animals, and histologic testing for N=1 pig at 3 months and N=1 pig at 6 months.

The 1.7 mm Mesh Suture prototype was designed to have tensile characteristics similar to USP size 0-polypropylene suture – used clinically in human abdominal wall closures. As the two devices being compared have similar tensile strength, any differences found in the UTS of the closure are due to biologic healing and not due to the strength of the device itself.

1.2.5. In Vitro Results

The data in the Figure 3 below shows that the 1.7 mm Mesh Suture prototype device closures were significantly stronger at 8 days than 0-polypropylene closures.

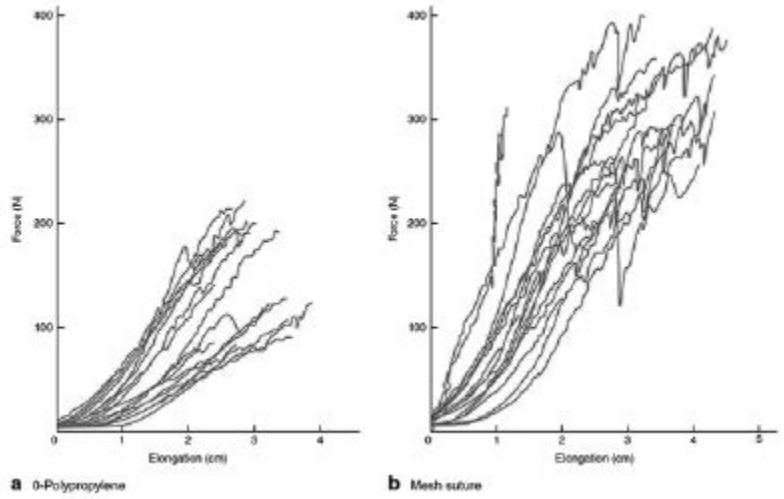


Figure 3: Porcine force/elongation curve data. Force and elongation comparison of explanted porcine abdominal wall segments with either Mesh Suture (n=16) or 0-polypropylene suture (n=18) 8 days after closure.

[3] **Dumanian GA**, Tulaimat A, Dumanian ZP. Experimental Study of the Characteristics of a Novel Mesh Suture. *Br J Surg.* 2015;102(10):1285-92.

1.2.6. In Vivo Results

Ultimate Tensile Strength (UTS)

The UTS for repaired *linea alba* was tested at 8 days. Failure was defined as the onset of muscle tearing. The UTS was defined as the highest force registered by the tensiometer. Elongation was defined as the distance that the tissue was stretched from the point where force rose above its baseline measurement until the UTS.

Work to UTS was computed as the product of force and elongation. Elasticity is defined as the force required to extend a material a unit distance. The elasticity for specimens was obtained from the slope of the linear portion of the force-elongation curves.

As shown in **Table 2**, the ultimate tensile strength was **double** and the work to failure (work is force times distance) was **triple** that of 0-polypropylene suture.

Table 2: Results from Porcine Model at 8 Days

Study Endpoint	Conventional Suture	Mesh Suture	p-value
Ultimate Tensile Strength (N)	160	320	$p < 0.001$
Work to Failure (J)	7	25	$p < 0.001$

Histology Testing

Histology testing at 8 days showed complete tissue integration of the mesh suture prototype. Histology at 90 and 180 days demonstrated a biocompatible tissue response and decreased device pull-through in comparison to standard 0-polypropylene suture. Small hernia defects were seen with the 0-polypropylene suture closures but not in the mesh suture closures. Relevant photographs of the porcine tissues post-op 3 months with polypropylene suture and the mesh suture prototype are shown in Figure 4. The polypropylene segment on the right has evidence of the suture cutting the fascia, while the entry points of the mesh suture prototype into the tissues are clean and without damage.

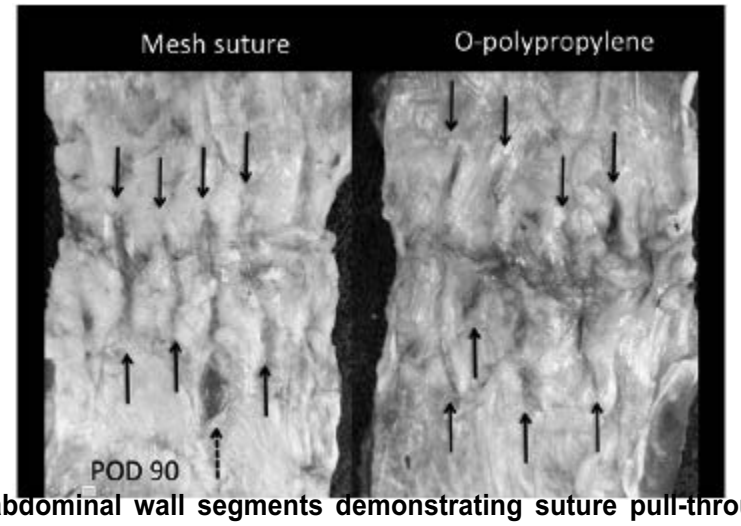


Figure 4: Porcine abdominal wall segments demonstrating suture pull-through with Mesh Suture and standard suture

1.2.7. Conclusion

A Mesh Suture reliably closed porcine laparotomies in human-sized animals. Tensile characteristics showed adequate strength of sutured segments, and histology demonstrated a characteristic tissue reaction for a macroporous implant.

1.3. Pre-clinical Dog Cadaveric Shoulder Study using Mesh Suture Prototype[4]

1.3.1. Objective

Characterize UTS of rotator cuff repairs, comparing a Mesh Suture prototype to 2 commonly used sutures.

1.3.2. Summary

This **independent** study was performed in the Department of Orthopedics at the Mayo Clinic in 72 cadaveric dog shoulders.

1.3.3. Background

Surgical repair is a common treatment for rotator cuff tear; however, the re-tear rate is high. A high degree of suture repair strength is important to ensure rotator cuff integrity for healing. The purpose of this study was to compare the mechanical performance of rotator cuffs repaired with a Mesh Suture versus traditional polydioxanone suture II and FiberWire sutures in a canine in vitro model.

1.3.4. Methods

Two suture techniques – simple interrupted sutures and two-row suture bridge – were used to reconnect the infraspinatus tendon to the greater tuberosity, using three different suture types: 1.7 mm diameter Mesh Suture prototype, polydioxanone suture II, or FiberWire. Shoulders were loaded to failure under displacement control at a rate of 20 mm/min. Failure load was compared between suture types and techniques.

1.3.5. Results

Ultimate failure load was significantly higher in the specimens repaired with Mesh Suture than with polydioxanone suture II or FiberWire, regardless of suture technique.

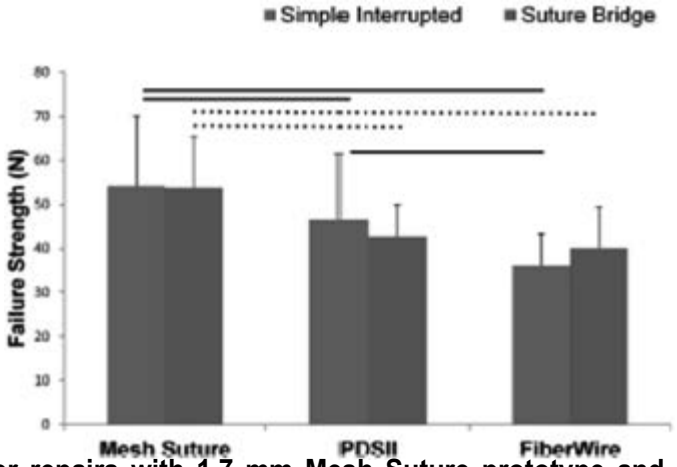


Figure 5: Dog shoulder repairs with 1.7 mm Mesh Suture prototype and standard sutures: Ultimate failure load of repaired tendon–bone interfaces. Solid lines indicate a significant difference between two groups in the simple interrupted suture technique and dotted lines indicate a significant difference between two groups in the suture bridge repair technique ($p < 0.05$).

1.3.6. Summary

Based on the biomechanical findings, rotator cuff repair with the Mesh Suture might provide superior initial strength against failure compared with the traditional polydioxanone suture II or FiberWire sutures. Use of the Mesh Suture may provide increased initial fixation strength and decrease gap formation, which could result in improved healing and lower re-tear rates following rotator cuff repair.

[4] Zhang T, Hatta T, Thoreson AR, Lu CC, Steinmann SP, Moran SL, Zhao C. Rotator cuff repair with a novel mesh suture: an ex vivo assessment of mechanical properties. *J Orthop Res.* 2018;36(3):987-992.

1.4. Pre-clinical Human Cadaveric Finger Tendon Study using 2-0 DURAMESH[5]

1.4.1. Objective

Characterize UTS of repaired cadaveric human finger tendons, comparing DURAMESH to two commonly used sutures.

1.4.2. Summary

This study was performed at the Department of Orthopedics at Loyola University and the Division of Plastic Surgery at Northwestern.

1.4.3. Background

Human finger flexor tendon repairs are known to be challenging procedures with high complication rates including adhesion formation, stiffness, and repair failure. While early motion protocols have demonstrated reduced adhesion formation and improved function, they place the repair site under tension and at risk of rupture. Conventional suture repairs, when stressed, fail as the suture cuts through the intervening tissue – known as "suture pull-through". The purpose of this study is to compare the biomechanical properties of flexor tendon repairs using a novel mesh suture device to traditional suture repairs.

1.4.4. Methods

Two suture techniques – simple interrupted sutures and two-row suture bridge – were used to reconnect the infraspinatus tendon to the greater tuberosity in human cadaveric samples, using three different suture types: 2-0 DURAMESH, polydioxanone suture II, or FiberWire. Shoulders were loaded to failure under displacement control at a rate of 20 mm/min. Failure load was compared between suture types and techniques. Sixty human cadaveric flexor digitorum profundus tendons were harvested and assigned to one of three suture repair groups: 3-0 and 4-0 braided poly-blend suture (FiberWire, Arthrex, Inc, Naples, FL), or 1 mm diameter mesh suture; all tendons were repaired using a 4-strand core cruciate suture configuration. Each tendon repair underwent either linear loading or cyclic loading until failure. Outcome measures included yield strength, ultimate strength, the number of cycles and load required to achieve 1 mm and 2 mm gap formation, and failure.

1.4.5. Results

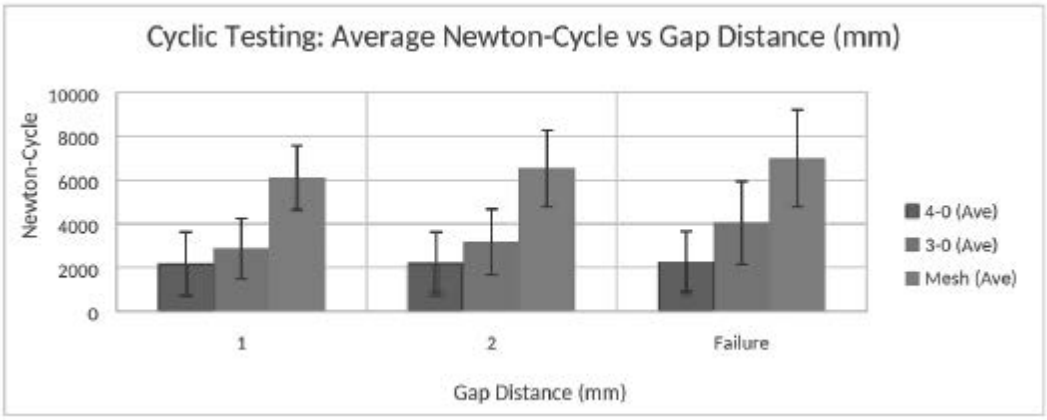
Mesh suture repairs had significantly higher yield and ultimate force values when compared to 3-0 and 4-0 braided poly-blend suture repairs under linear testing. The average force required to produce repair gaps was significantly higher in mesh suture repairs compared to conventional suture. Mesh suture repairs endured a significantly greater number of cycles and force applied before failure compared to both 3-0 and 4-0 conventional suture.

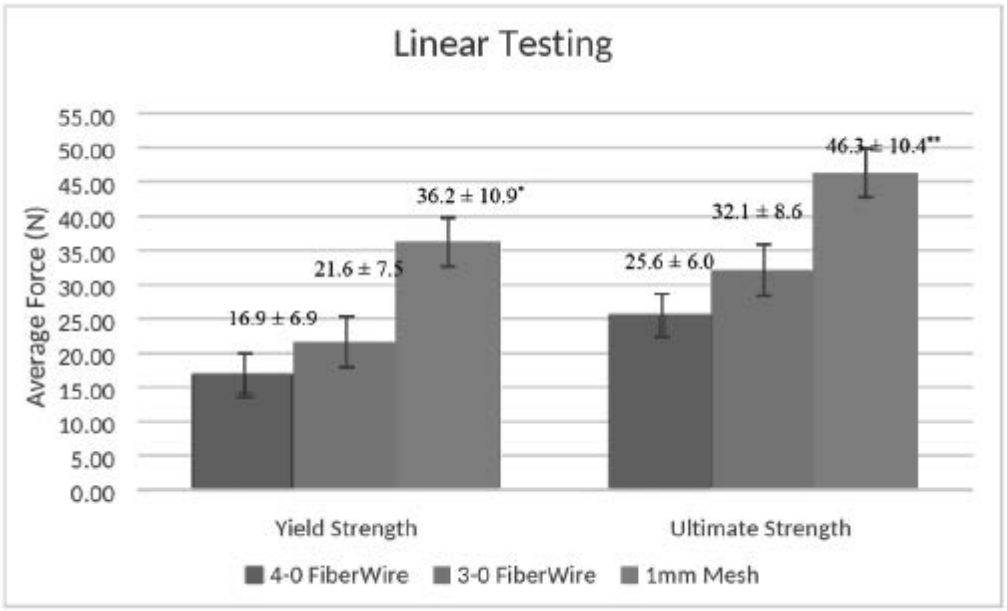
1.4.6. Summary

This biomechanical study of flexor tendon repairs using a novel mesh suture reveals significant increases in average yield strength, ultimate strength, and average force required for gap formation and repair failure with mesh suture repairs compared to conventional suture cohorts. Such findings could allow for earlier mobilization, decreased adhesion formation, and lower rupture rates after flexor tendon repairs.

---

[5] Wallace SA, Mioton LM, Havey RM, Muriuki MG, Ko JH. Biomechanical properties of a novel mesh suture in a cadaveric flexor tendon repair model. Submitted for publication to *J Hand Surg*.





* Mesh suture had significantly higher average yield strength compared to both 4-0 and 3-0 FiberWire, p <0.001 and p=0.003 respectively

Figure 6: Cyclic and linear testing of 2-0 DURAMESH and Standard Sutures for repairing human cadaveric finger flexor tendons

2. SUPPORTING CLINICAL LITERATURE STUDIES

Years ago, Dr. Dumanian developed a new closure technique for human abdominal wall defects. Strips of macroporous polypropylene mesh were cut from a sheet of mesh and used as a suture for soft tissue approximation. This clinical concept of utilizing strips of polypropylene mesh as a suture led to the Improved Suture Patent (US 2013/0226232 A1), Advanced Suture Inc. (www.meshsuture.com), and development of the DURAMESH, the subject of this 510(k) application. Mesh strips for closure of abdominal wall defects were published in two clinical articles attached with this 510(k) submission as a supporting clinical study to the concept of a low filament size/high surface area closure. Since Dr. Dumanian first reported on his technique for Mesh Sutured Repairs of Abdominal Wall Defects, the technique has gained acceptance by the surgical community. Mesh Sutured repairs have been used successfully in hundreds of cases at numerous institutions including Northwestern, The Ohio State University, Memorial Sloan Kettering, the University of Illinois Chicago, and Walter Reed. The technique was recently summarized in proceedings from an international hernia prevention symposium.[6]

2.1. Mesh Sutured Repairs of Abdominal Wall Defects[7]

2.1.1. Background

Planar meshes are known to improve outcomes of incisional hernia repair. Planar meshes distribute forces across high tension closures such as laparotomy incisions. Fibrous ingrowth between and around filaments helps increases the strength of the repair. However, the use of planar mesh is not without drawbacks, due to the increased amount of foreign material, infections, extrusions, and soft tissue devascularization to place the devices.

2.1.2. Methods

A new technique for abdominal wall closure was devised that uses strips of mesh as sutures. The mesh strips from a single piece of Prolene Soft Mesh (Ethicon, Somerville NJ) were cut 20-mm wide along the blue lines and passed through the tissues with a clamp. The mesh strips are tied with knots to achieve tissue apposition. This technique was used in a total of 107 patients for a wide range of abdominal wall defects.

2.1.3. Results

Of the 107 patients, 76 had preoperative hernias, and the mean hernia width by CT scan for those with scans was 9.1 cm. The remaining 31 patients had abdominal closures with mesh strips due to non-midline defects, for the desire to have a small procedure and avoid planar mesh, or for patients with open abdomens after trauma. Forty-nine surgical fields were clean-contaminated, contaminated, or dirty. Five patients had infections within the first 30 days. Only one knot was removed as an office procedure. Mean follow-up at 234 days revealed 4 recurrent hernias.

2.1.4. Conclusions

Lessons learned from these patients include:

---

[6] Harris HW, Hope WH, Adrales G, Andersen DK, Deerenberg EB, Diener H, **Dumanian G**, East B, Fischer JP, Urena MAG, Gibeily GJ, Hansson BM, Hernandez-Granados P, Hiles MC, Jeekel J, Levinson H, Lopez-Cano M, Muysoms F, Pereira JA, Prudhomme M, Ramaswamy A, Stabilini C, Torkington J, Valverde S, Young DM. Contemporary concepts in hernia prevention: Selected proceedings from the 2017 International symposium on prevention of incisional hernias. *Surgery.* 2018;164(2):319-326.

[7] Lanier ST, **Dumanian GA**, Jordan SW, Miller KR, Ali NA, Stock SR. Mesh sutured repairs of abdominal wall defects. *Plast Reconstr Surg Glob Open.* 2016;4(9):e1060.

a. Despite placing these strips into contaminated fields in 49 patients, there were few knots that needed to be removed, and no patient returned to the operating room for the removal of a deep infected knot.
b. The overall surgical site occurrence (SSO) and surgical site infection (SSI) rate was low considering the complexity of the patient population
c. The overall amount of foreign material in comparison to the use of planar mesh is much reduced. Maintenance of tissue vascularity and the rapid incorporation of the mesh strips was postulated to be a reason for the favorable outcomes.
d. Bowel adhesions were not a clinical problem seen in these patients.
e. In patients with open wounds in whom both 0-polypropylene sutures and mesh strips were used, the sutures would have to be removed, while the strips granulated over and closed with minimal wound care. Improved biocompatibility was theorized to be due to the smaller diameter filaments that comprise the mesh strips (100 μm) as opposed to the 0-polypropylene sutures (400 μm).

2.2. Mesh Sutured Repairs of Contaminated Incisional Hernias[8]

2.2.1. Background

There is no surgical consensus for the closure of an incisional hernia in the presence of contamination. While planar meshes can be successfully used, any infection or need for re-operative bowel surgery requires a sizeable procedure to remove the sheet of mesh. Bioprosthetic meshes do not seem to provide durable hernia closure and are expensive. In this retrospective study, the safety and efficacy of using strips of mesh as sutures was investigated.

2.2.2. Methods

48 patients with contaminated hernias 5-cm wide or greater by CT scan were closed with strips of mesh. Surgical site occurrence (SSO), surgical site infections (SSI), and hernia recurrence were compared to similar patient series reported in the literature.

2.2.3. Results

Of the 48 patients, 20 had clean-contaminated wounds, 16 had contaminated wounds, and 12 were infected. 69% of the patients underwent an anterior perforator sparing components release for hernias that averaged 10.5 cm transversely (range 5 cme25 cm). SSO occurred in 27% of patients while SSI was 19%. There were no fistulas or delayed suture sinuses. With a mean follow-up of almost 12 months, 3 midline hernias recurred (6%). In these same patients, three parastomal hernias repaired with mesh sutures failed out of 4 attempted for a total failure rate of 13%.

2.2.4. Conclusions

Closure of contaminated incisional hernias is not only possible with a mesh suture, but it is preferable when compared to other techniques in the literature including simple suture closure, planar prosthetic mesh, and planar bioprosthetic mesh. Direct closure of the abdominal wall maintains tissue vascularity, decreases the total amount of prosthetic material used, saves tissue planes for another day, can be performed by surgeons of all disciplines, and is rapid.

[8] **Dumanian GA**, Lanier ST, Souza JM, Young MW, Boller AM, Mueller KH, Halverson AL, McGee MF, Stulberg JJ. Mesh sutured repairs of contaminated incisional hernias. *Am J Surg.* 2018;216(2):267-273.

Table 3
Comparison to the literature.

Author, year	Dumanian, 2017	Carbonell, 2013	Slater, 2013	Rosen, 2017	Itani, 2012	Atema, 2017
Number of subjects	48	100	81	104	80	60
Technique	Mesh Suture	Retro-rectus polyporopylene	Polypropylene	BioA	Strattice	Strattice
CDC 2	20 (40%)	42 (42%)	34 (43%)	24 (23%)	39 (48.7%)	NR
CDC 3	16 (36%)	58 (58%)	19 (23%)	80 (77%)	39 (48.7)	NR
CDC 4	12 (24%)	0	28 (35%)	0	2 (2.6%)	NR
VHWG 3	37 (77%)	NR	NR	NR	69 (75%)	66 (83%)
VHWG 4	11 (23%)	NR	NR	NR	20 (25%)	14 (17%)
Age	62.4 ± 14.5	60 ± 13	58.6	58	57 ± 14	63
BMI	29.5 ± 7.4	32 ± 9.3	26.6	28	NR	27.8 ± 5.9
Components separation	69%	49%	100	65%	65%	68%
SSO	27%	31%	52%	28%	66%	NR
SSI	19%	18%	19%	18%	35%	45%
Return to operating room	10%	12%	11.7	NR	NR	4%
30-day readmission	6%	NR	NR	NR	NR	28%
Hernia recurrence	13%	7%	NR	17%	28%	13%
Mean follow-up (months)	11.8	10.8	NR	24	24	7

CDC: Centers for Disease Control.
VHWG: Ventral Hernia Working Group.
BMI: body mass index.
SSO: Surgical site occurrence.
SSI: Surgical site infection.

Signed Revision of CIP

Dr. Garen Koloyan
PI
Wigmore Clinic

April 19, 2019

Dr. Greg Dumanian
Science Officer
Mesh Suture

April 19, 2019