Title: Multi-Institutional Randomized Controlled Trial Evaluating Use of Arista Absorbable Surgical Hemostatic Powder in Anterolateral Thigh Donor Sites

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RESEARCH PROPOSAL

Multi-Institutional Randomized Controlled Trial evaluating use of Arista Absorbable Surgical Hemostatic Powder in Anterolateral Thigh Donor Sites

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0.0 STUDY AIMS AND OBJECTIVES

This is a single-blinded multi-institutional randomized controlled trial to evaluate the effectiveness of Arista hemostatic matrix powder (Arista® AH, C. R. Bard, Inc. Davol, Warwick, RI) in reducing drainage output in anterolateral thigh (ALT) free flap donor sites. Increased drainage from donor sites can lead to seroma formation with possible secondary infection, delayed hospital discharge, and additional home care needs for drain care. Arista is an inert plant based absorbable surgical hemostatic powder that can be easily applied to broad surgical fields to reduce bleeding and seroma rates. Therefore, its application to free flap donor sites may bear significant potential benefit.

Specific Aim 1: The main hypothesis of the study is that the use of Arista in anterolateral thigh (ALT) free flap donor sites prior to closure will reduce postoperative drain outputs and time to drain removal compared to ALT donor sites closed without Arista.

Specific Aim 2: This study will also evaluate the secondary hypotheses that Arista will reduce postoperative ALT donor site seromas and patient hospital length of stay.

1.0 INTRODUCTION

Free tissue transfer is a commonly performed procedure, especially at tertiary care hospitals. In free tissue transfer, "spare tissue" from one area of the body (donor site) is re-implanted to an area that is need of reconstruction (defect site). When relocated, the "spare tissue" is given vitality and blood supply at its new location by microscopically sewing and connecting its feeding artery and vein to an artery and vein in or near the defect site. Hence, this operation is referred to as "microvascular free tissue transfer" or "free flap". Defect sites most commonly result from tumor or cancer removal and trauma related injuries. Free flaps are frequently used to reconstruct breast tissue after mastectomy, head and neck cancer resections, extremity injuries, and chronically infected wounds. The indications, utilization, and expertise in free flap surgery continue to grow, providing patients with enhanced outcomes of otherwise difficult cancers and wounds.

Since its original description in 1984 the ALT microvascular free flap has become an increasingly integral part of head and neck reconstructive surgery.[1, 2] ALT free flaps have been shown to be a reliable method for several reconstructive procedures with minimal donor site morbidity.[2-4] The ALT free flap is composed of skin, subcutaneous tissue, and fat of the anterolateral thigh. The blood supply to this area is from the lateral circumflex femoral artery and vein (**Figure 1**). These vessels along with the tissues of the anterolateral thigh are carefully dissected and removed as a single unit to be re-implanted in a different part of the body (**Figure 2**).

Figure 1. Anterolateral thigh free flap anatomy.

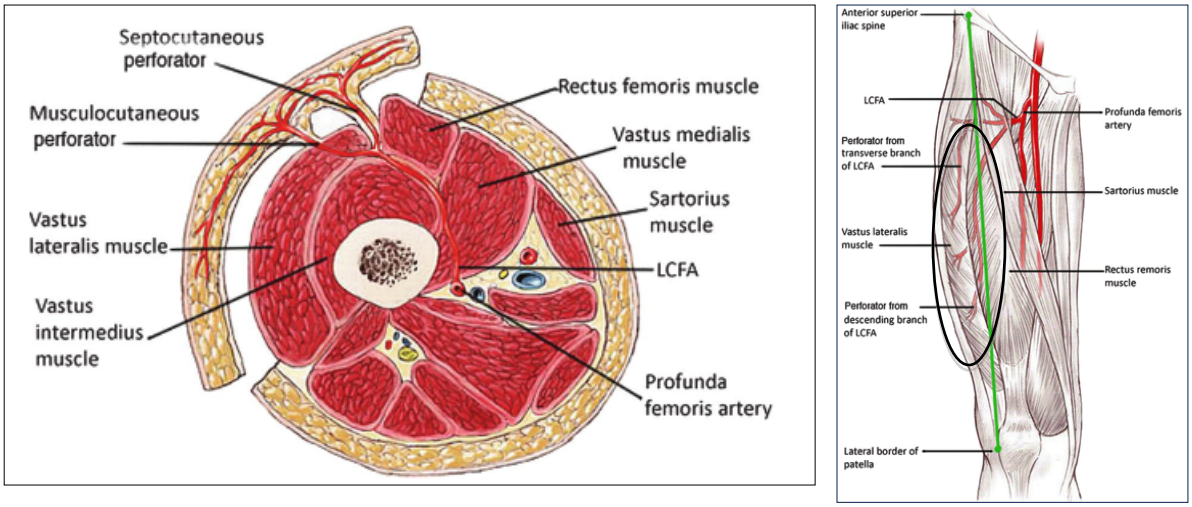
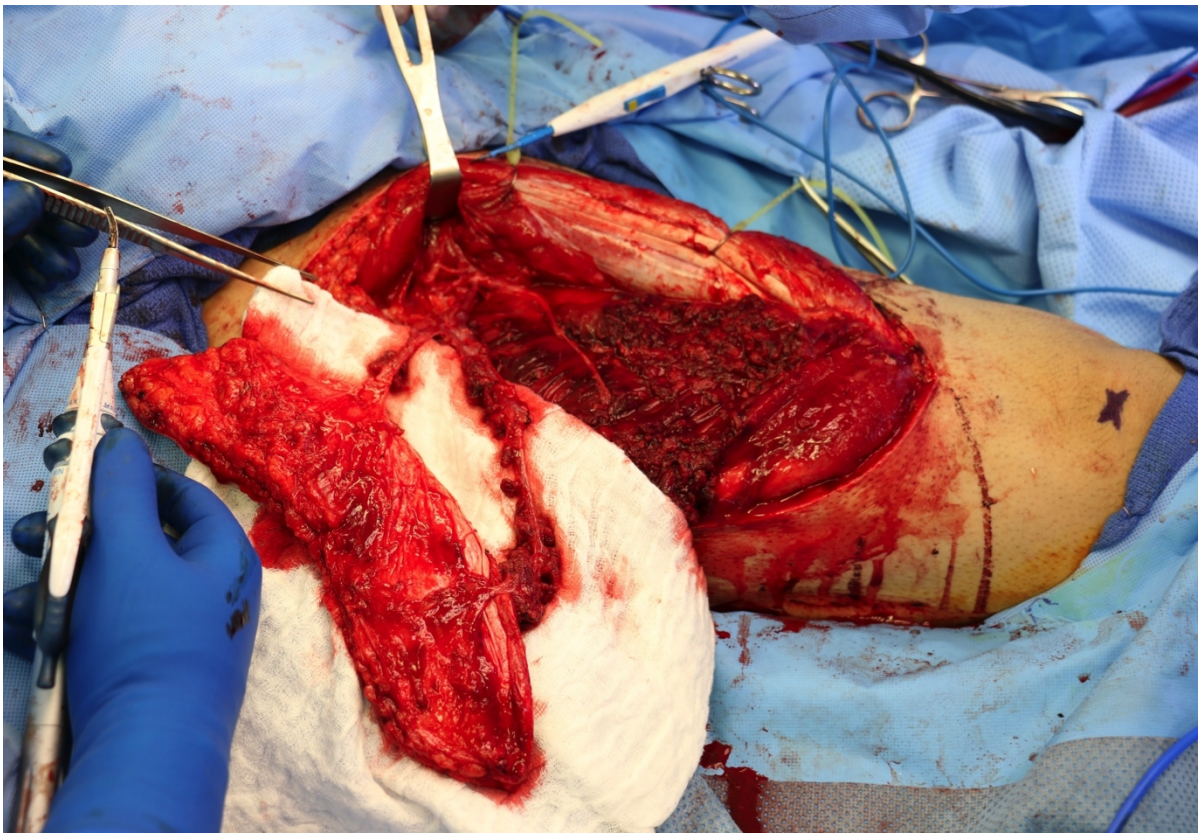


Figure 2. Anterolateral thigh free flap dissection, showing flap and LCFA feeding vessels.



Multiple options exist for soft tissue free flap donor sites similar to the ALT. However, a distinct advantage of the ALT free flap over others is the minimal donor site morbidity that the patient undergoes. Patients are able to fully ambulate and function after the surgery, and are left with only a well-healed scar line. Despite its many advantages, postoperative fluid collections continue to be problematic in the ALT donor site. Studies have reported seroma rates in ALT donor sites as high as 5% although this likely underestimates the true incidence of clinically significant postoperative fluid collections and wound complications in this patient population.[2] ALT free flaps require a large amount of tissue dissection and removal, creating a large potential space in the lateral thigh that often requires prolonged postoperative suction drainage and pressure dressings in efforts to minimize fluid accumulation.

Research in optimal postoperative management for the ALT donor site is lacking. Current management without the use of Arista often requires a surgical drain for 7-14 days, which can delay patient discharge and expose patients to increased risk of postoperative wound infections. There is a paucity of data on methods to reduce ALT donor site drain output and seromas. Surgeons often use a combination of closed suction surgical drains and pressure dressings to try and reduce the amount of fluid collection in the thigh donor sites. Although this does provide some advantage, if these techniques are required for a prolonged time, unnecessary hospital stay and patient morbidity are attained. According the Healthcare Cost and Utilization Project, an average inpatient hospitalization in 2009 cost $2,000 per day, and is increasing.[5] If the use of a single bottle of Arista could reduce just 1 hospital day per patient it could save at least $80,000 dollars a year at our department alone. Further, the associated morbidity and health care costs of potential seroma or infected seroma complications may be avoided.

A randomized controlled trial aimed at evaluating improved methods to reduce postoperative drainage from ALT donor sites could provide critical information on how to best serve our patients, eliminate

unnecessary hospital stay, and reduce overall cost. Once studied in a controlled single flap environment, these methods could be then expanded to other or all free flap donor sites.

According to the manufacturer, Arista uses Microporous Polysaccharide Hemospheres (MPH) technology to catalyze the clotting cascade and effectively dehydrate tissue to initiate hemostasis in broad areas. Major advantages of Arista are that it has been shown to be safe and effective across multiple surgical disciplines, is completely absorbed in 24-48 hours, and contains no human or animal components.[6-8]

Sindwani *et al.* was the first to report effectiveness and safety of Arista as a hemostatic agent in otolaryngology demonstrating its application in controlling postoperative bleeding after endoscopic sinus surgery.[8] Zhang *et al.* demonstrated success rate of 100% in the prevention of seromas in patients undergoing resection of malignant tumors in multiple locations, including the lower extremity.[7] Arista was recently shown to be useful in reducing postoperative chest tube output and hemostasis time in patients undergoing cardiothoracic surgery.[6]

These previous works support the idea that Arista could be effective in reducing postoperative fluid collection and drainage time in free flap donor sites. However, this would be a new application of Arista with wide applicability that has not been previously described.

1.1 Research Rationale and Possible Influence On Clinical Practice

Reconstructive surgery has evolved in a recent era of increased attention to patient satisfaction and cost savings. The ALT free flap has been proven to be highly successful; however, optimal management of the donor site postoperatively is an area in need of additional gains via research. Decreasing free flap donor site drain output and earlier drain removal could improve the quality of life of our patients, significantly decrease the cost of their care, and potentially decrease drain-associated infections. If this study were to demonstrate Arista to reduce postoperative donor site drainage and seroma rates and/or a decrease in hospital length of stay resulting from early surgical drain removal, it could dramatically affect the way we take care of our patients.

This study seeks to critically evaluate current clinical practice paradigms to better understand the influence of Arista use in free flap donor sites. A prospective, multi-institutional, randomized, controlled, single-blinded trial is the clearest methodology to evaluate the possible benefits of Arista. Additionally, study in the ALT free flap alone, a single and commonly performed free flap, limits bias and confounding variables. No clinical trial of this level has been performed on this topic; thus, our proposal is novel and the findings of the study are potentially important.

2.0 SUBJECTS AND METHODS

2.1 Patient Population and Enrollment

All adult patients (18 years old and over) undergoing ALT reconstruction by one of three microvascular-trained Head and Neck Surgery faculty members at UCSF and a single microvascular-trained Head and Neck surgeon at Cleveland Clinic's Head and Neck Institute will be included in enrollment for the study and consecutively registered.

Exclusion criteria will consist of patient age under 18, requirement of postoperative anticoagulant medications other than routine deep venous thrombosis prophylaxis (such as warfarin), and presence of clotting or bleeding disorder.

Approval from the intuitional review board (IRB) of both UCSF and Cleveland Clinic will be required prior to initiation of enrollment. (IRB submission pending but expected in next several weeks.) Patients eligible for inclusion in the IRB approved study will be approached for study enrollment. Written consent

will be discussed with the patient by the approved study investigators and/or research assistants. Further details are provided below (Section 3.0 Patient Selection).

2.2 Study Protocols and Surgical Description

If successfully enrolled to the study, a randomized packet containing the patient's research ID number will be pulled and included into the patient's chart. Randomization will be done at the initiation of the study by creating a randomization list with blocking and stratification by surgeon. An envelope containing the patients randomized group assignment will not be opened until the end of ALT free flap harvest just prior to closure.

The patients will be randomized to one of two groups. Patients in Group 1 will have 5 grams of Arista applied diffusely to the wound bed before primary closure (**Figure 3**). Per routine, a single 10 French Jackson-Pratt drain is placed within the wound bed and is removed per a standardized protocol agreed upon by the study surgeons. All thigh donor sites will be closed in 2 layers with 3-0 vicryl for the deep dermis, and either 5-0 fast-absorbing running suture, 4-0 nylon suture, or staples for the superficial skin, depending on surgeon preference. The thigh is circumferentially wrapped with an Ace wrap dressing. Group 2 will have identical closure and drain management, except without the use of any Arista. Patients in both treatment groups obtain routine deep venous thrombosis prophylaxis with either weight-based subcutaneous heparin or enoxaparin during the postoperative period. All patients will receive standardized postoperative orders and care (**Figure 4**).

Figure 3. Arista application (5 grams) to anterolateral thigh free flap donor site.

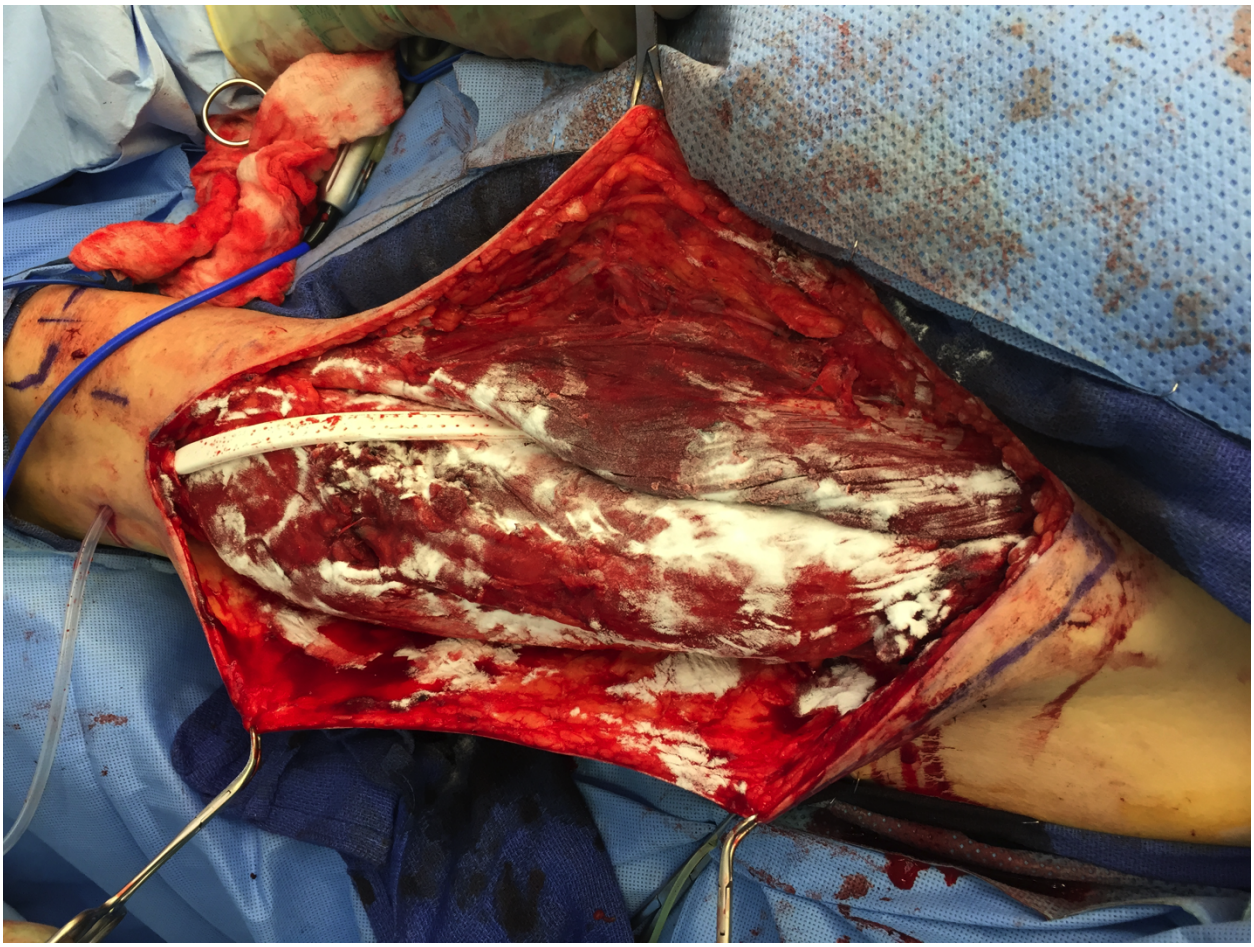
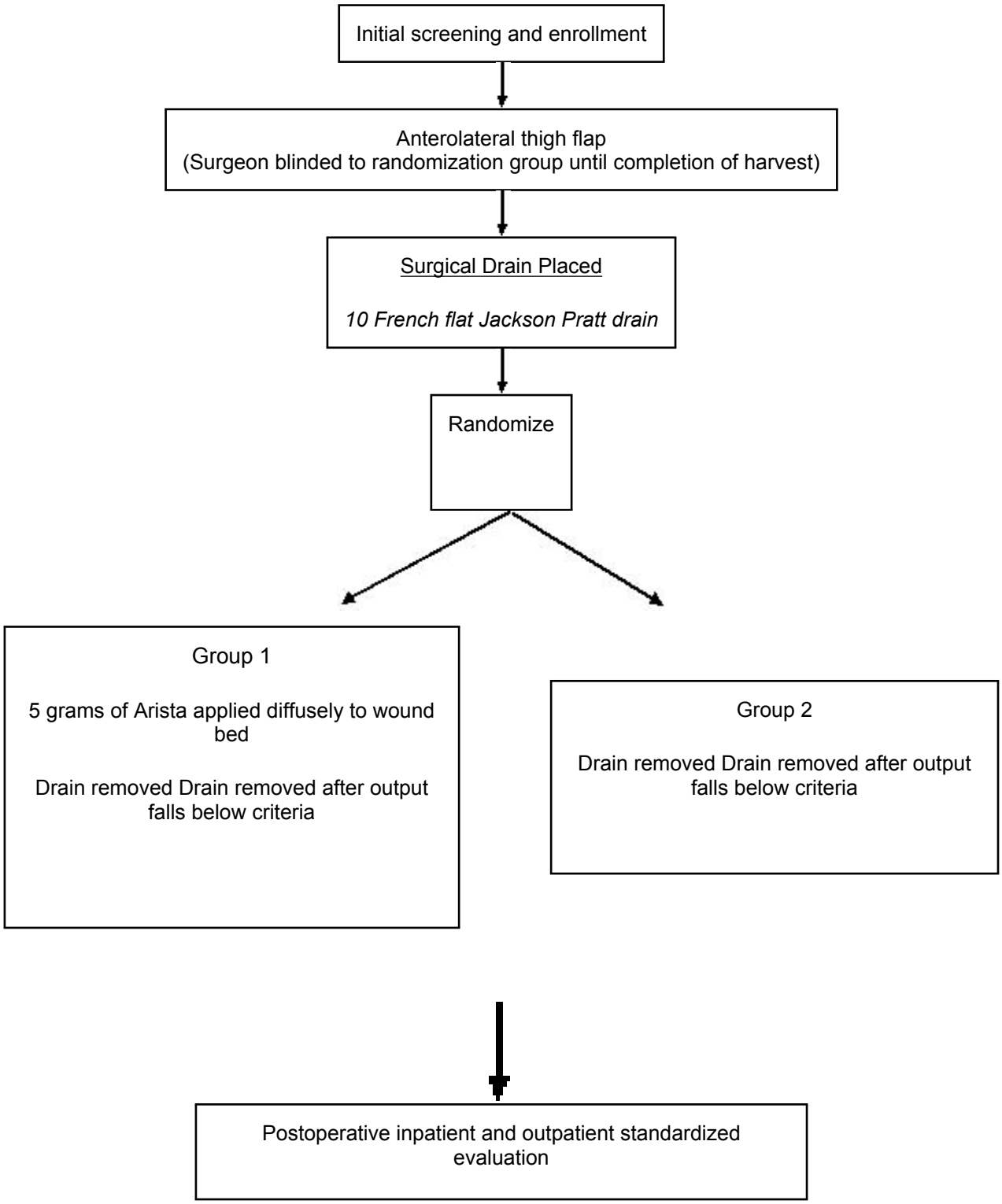


Figure 4. Study schema



Postoperative care will be standardized between both institutions. A standardized physical exam will be performed on all patients each day of the inpatient stay, which is typically 4-10 days depending on a multitude of factors. After hospital discharge, the patient will be evaluated in the outpatient clinic, typically approximately 14 days after the surgery. During all clinical examinations, inpatient and outpatient, the ALT free flap donor site is evaluated for clinical evidence of seroma, hematomas, incision breakdown, and infection. Drains will be stripped and outputs recorded every 8 hours until removed. Patients are encouraged to begin ambulation on the first day after surgery. The Ace wrap is used for the first 2 weeks after surgery.

Specifically, the physical exam will include:

1. Inspect and palpate for presence fluctuance or fluid collection.
2. Inspect for color change, erythema or ecchymosis.
3. Inspect the incision line.
4. Palpate for tenderness.
5. Strip the drain and ensure that it is adequately functioning.
6. Re-application of Ace wrap.

The drain will only be removed per protocol, according to postoperative day and amount of recorded 24-hour drainage output (**Table 1**). Inpatient and outpatient drain management are outlined. Typically, patients remain as an inpatient in the hospital until discharge on postoperative day (POD) 7-10. The drain is not removed for the first 3 days. After that time, the drain is kept until the output drops to a level that may allow for the drain to be safely removed. This is a factor dependent on the POD and amount of drain output per 24 hours, as outlined in **Table 1**.

All patients will receive similar postoperative instructions including wound care, with and without drain. If the patient requires the drain to remain intact in the thigh at time of discharge, the patient is fully instructed on drain care, emptying, and recording. The patient is then seen in the outpatient clinic, typically at approximately 7-14 days after the surgery, the drain is removed regardless of output.

Table 1. Drain Management Protocol.

Postoperative Day (POD)	Removal Criteria
Inpatient	
POD 0 - 3	Drain is not removed.
POD 4 - 7	Drain output ≤ 30mL in previous 24 hours.
On day of discharge	Drain output ≤ 60mL in previous 24 hours.
POD > 7	Drain output ≤ 60mL in previous 24 hours.
On day of discharge	Drain output ≤ 100mL in previous 24 hours.
Outpatient	
POD ≤ 7	Drain may be removed if output is ≤ 60mL in previous 24 hours.
POD > 7	Drain is removed regardless of output.

2.3 Primary Endpoints and Outcomes

The primary outcome analyzed in this study will be total drain output (mL) in an effort to determine if the addition of Arista to the wound bed decreases overall wound drainage and drain output. Given that drain output influences time of drain removal, assessment will be made to determine if timing of drain removal differs between groups.

2.4 Secondary Endpoints

Secondary outcomes will allow for a robust analysis and will include:

1. Development of ALT donor site hemoatoma.
2. Development of ALT donor site seroma.
3. Requirement of patient to be discharged with drain.

4. Hospital length of stay.
5. Need for any additional procedures to the ALT donor site secondary wound complications.

3.0 PATIENT SELECTION

3.1 Registering Patients

Eligibility will include consecutively seen adult patients in the Department of Otolaryngology-Head and Neck Surgery at the University of California-San Francisco (UCSF) and the Cleveland Clinic's Head and Neck Institute who will be undergoing ALT free flap reconstruction. Inclusion and exclusion criteria are described previously (Section 2.1 Patient Population and Enrollment). Patients will be enrolled in the study after completing the eligibility checklist and signing the study-specific consent form at the preoperative appointment. The study will be multi-institutional and conducted at UCSF and Cleveland Clinic. These two sites are chosen due a strong relationship bearing established partnership in multiple previous projects, along with similar practices, techniques, and patient management strategies.

3.2 Specific Conditions for Patient Eligibility

3.2.1 Patients undergoing ALT free tissue transfer for head and neck reconstruction
3.2.2 Patient must be 18 years of age or older.
3.2.3 The patient must have capacity to be able to sign a study-specific informed consent prior to study entry.

3.3 Conditions for Patient Ineligibility

3.3.1 Pregnancy (for female patients).
3.3.2 Patients who will require anticoagulant medications other than routine DVT prophylaxis within 8 days postoperatively.
3.3.3 Presence of clotting or bleeding disorder.

3.4 Randomization

After the ALT free flap is dissected and harvested, the patients will be randomized into two groups:
- Intervention group (Group 1): 5 grams of Arista applied diffusely to wound bed prior to closure + standard postoperative management.
- Control group (Group 2): Standard postoperative management without the use of Arista.

3.5 Blinding

The Surgeons will be blinded to the randomization group of the patients until after the ALT has been harvested.

4.0 STATISTICAL ANALYSIS and REPORT

4.1 Statistical Methods

All statistical analysis will use intention to treat and a two-tailed test with 0.05 level for significance. The primary outcome of this study will be total drain output. This is a continuous variable that will be evaluated with the Wilcoxon rank-sum test.

Secondary outcomes will be the hospital length of stay (Wilcoxon rank-sum test), days until drain removal (Wilcoxon rank-sum test), the need for any additional procedures (Fisher's exact test), and the presence or absence of seromas/hematoma (Fisher's exact test).

4.2 Target Enrollment and Sample Size

We estimate the necessary sample size to be 50 patients with 25 in each group to detect a 20% decrease in total drain output with 0.05 significance level and 0.8 power assuming an average total drain output of 500ml. To achieve the sample size of 50 patients, with 5 patients per month accrual, we expect this study to take approximately 1 year to accrue the required sample of patients and submit a manuscript.

4.3 Study Timeline

Given results of the grant process are provided July 15, 2015, we estimate ability to start the study by September 1, 2015. The study will take approximately 1 year to perform. Two months may be required for study statics, drafting/revisions of the manuscript, and manuscript submission. Therefore, we anticipate submission to an academic peer-reviewed journal by the end of 2016.

4.4 Publication Plans

Given the paucity of data in this area and our study design, we expect publication in an accredited peer-reviewed journal. Potential journals would have focus areas of microvascular free flap reconstruction, including *Plastic & Reconstructive Surgery*, *JAMA Facial Plastic Surgery*, *Head & Neck*, *Otolaryngology Head and Neck Surgery*, *Journal of Microvascular Surgery*. Given the above study timeline, we anticipate manuscript preparation to be complete and journal submission by the end of 2016.

5.0 PERSONNEL

Special personnel required for this study have been addressed (e.g. subspecialists, technicians, etc.):

None. Subspecialists required for this study are already party of the multidisciplinary head and neck and microvascular surgery team.

Sufficient support staff available for study completion:

Yes. Research assistants, medical assistants, nurses, and physician assistant in head and neck surgery with assist in patient accrual and data analysis

Who will do your consenting, data & sample collection, and regulatory?

Consenting: Dr. Rahul Seth, Dr. P. Daniel Knott, Dr. Chase Heaton, Dr. Michael Fritz, Dr. Matthew Tamplen, and other IRB-approved research assistants and physician assistants.

Data and sample collection: Dr. Rahul Seth, Dr. P. Daniel Knott, Dr. Chase Heaton, Dr. Michael Fritz, Dr. Matthew Tamplen, and other IRB-approved research assistants.

Regulatory: Dr. Rahul Seth and research assistants.

6.0 BUDGET

INTERNAL DOCUMENT

Industry Sponsored Clinical Trial Study Summary

Study Title:	Multi-Institutional Randomized Controlled Trial evaluating use of Arista Absorbable Surgical Hemostatic Powder in Anterolateral Thigh Donor Sites
Sponsor:	Bard Davol
Protocol Number:	Arista
Principal Investigator:	Rahul Seth, M.D

IDC RATE	
0%	Department Fee %
33%	Institutional Overhead %

Payment Categories	Payments	
NON-REFUNDABLE START-UP PAYMENTS	$ 10,973	
ALL STUDY ARM PAYMENTS	$ 45,486	
ALL VARIABLE PAYMENTS	$ 4,057	
CLOSE-OUT PAYMENTS	$ 1,456	
Award Total, Estimated	$ 61,971	
OSR Form Breakdown	$ 46,595	Directs
	$ 15,376	Indirects 33%

NON-REFUNDABLE START-UP PAYMENTS	Charges	Dept. Fee	Dept. Total Directs	Institutional OH	Payment
UCSF Initial IRB Review Fee	$ 2,700	$ -	$ 2,700	$ 891	$ 3,591
Cleveland Clinic Start Up Fee	$ 1,950	$ -	$ 1,950	$ 644	$ 2,594
Cleveland Clinic IRB Submission Fee	$ 2,600.00	$ -	$ 2,600	$ 858	$ 3,458
UCSF Investigational Pharmacy Set-Up Fee	$ 1,000	$ -	$ 1,000	$ 330	$ 1,330
					$ 10,973

ALL STUDY ARM PAYMENTS	Charges	Dept. Fee	Dept. Total Directs	Institutional OH	Payment	Estimated #	Estimated Payments
Per Patient Payment (Study Personnel Costs)	$ 684	$ -	$ 684	$ 226	$ 910	$ 50	$ 45,486
							$ 45,486

ALL VARIABLE PAYMENTS	Charges	Dept. Fee	Dept. Total Directs	Institutional OH	Payment	Estimated #	Estimated Payments
UCSF IRB Annual Review Fee	$ 1,200.00	$ -	$ 1,200	$ 396	$ 1,596	1	$ 1,596
UCSF Investigational Pharmacy Annual Maintenance Fee	$ 200.00	$ -	$ 200	$ 66	$ 266	1	$ 266
UCSF Investigational Pharmacy Dispensing Fee	$ 20.00	$ -	$ 20	$ 7	$ 27	50	$ 1,330
Cleveland Clinic Renewal Fee	$ 650.00	$ -	$ 650	$ 215	$ 865	1	$ 865
							$ 4,057

CLOSE-OUT PAYMENTS	Charges	Dept. Fee	Dept. Total Directs	Institutional OH	Payment
UCSF Investigational Pharmacy Closure Fee	$ 250	$ -	$ 250	$ 83	$ 333
Cleveland Clinic Study Close Out Fee	$ 845	$ -	$ 845	$ 279	$ 1,124
					$ 1,456

6.1 Budget Justification

Support is in place from the Departments of Otolaryngology-Head and Neck Surgery at UCSF and CCF to carry out initial enrollment and data collection; however, additional funds are necessary and the study would not be possible without additional support from Bard, Inc as listed above.

Supplies

None needed.

Travel Expenses

None requested.

Other Costs

Inclusive of standard fees for institutional IRB approval of an industry supported trial. Other fees are standard costs associated with all grant funding at UCSF.

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Multi-Institutional Randomized Controlled Trial evaluating use of Arista Absorbable Surgical Hemostatic Powder in Anterolateral Thigh Donor Sites

This is a clinical trial, a type of research study. Your study doctor(s), Dr. Rahul Seth, Dr. Chase Heaton, Dr. P. Daniel Knott, from the Department of Otolaryngology will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have will be undergoing the type of reconstructive surgery we would like to study.

Why is this study being done?

The purpose of this study is to evaluate the effects, good and/or bad, of an absorbable product known as Arista in your leg site.

Background: Many patients undergo a similar leg surgery and it very common to place a small drain in your leg after the procedure is completed to drain any residual fluid. Arista is a plant based starch product used to try and reduce the amount of residual fluid that needs to be drained in effort to reduce total drain output and days needed with drain in place The drain comes out of a small hole in your skin and the nursing staff records the output. The timing of drain removal is often variable and depends on the amount of fluid recorded. This study will evaluate the potential benefit of arista on timing of drain removal.

How many people will take part in this study?

Approximately 50 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the main part of the study...

You will be selected as a candidate based on the operation you will be having.

During the main part of the study...

- You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

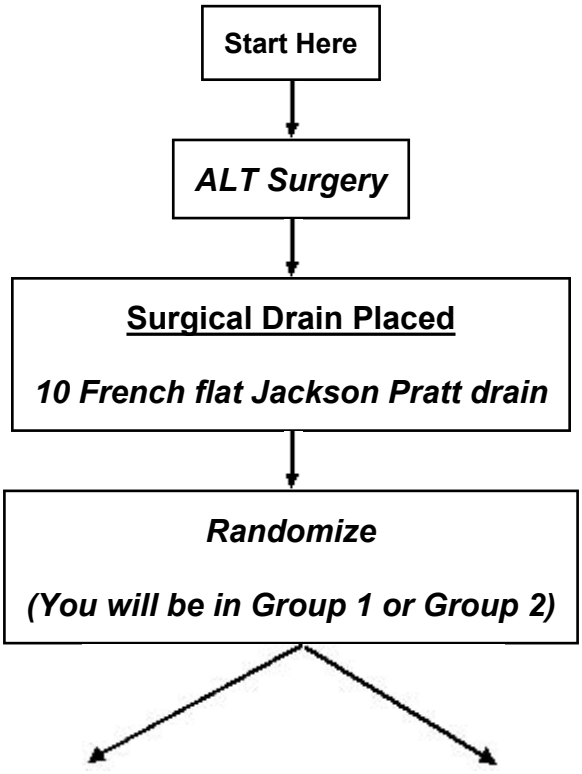
    - **If you are in group 1:** Arista will be used in your leg site
    - **If you are in group 2:** Arista will not be used in your drain site

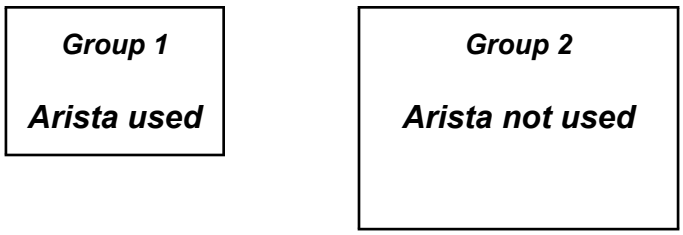
When you are finished with your surgery:

You will receive the same high quality care in everyway. The only difference will be the use of Arista in your leg wound. You will be closely monitored by our inpatient team as well as followed in a postoperative appointment.

- **Study location:** All study procedures will be done at UCSF

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.





How long will I be in the study?

You will be asked to take part in this study during your stay in the hospital and come to your first postoperative appointment, The study doctor will ask you to visit the office for follow-up exam one week after discharge from the hospital.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects.

You should talk to your study doctor about any side effects you experience while taking part in the study.

Risks and side effects related to the study include:

Likely

- None

Less Likely

- No side effects have been reported with Arista use in several peer-reviewed studies.

Rare but serious

- No side effects have been reported with Arista use in several peer-reviewed studies.

- **Randomization risks:** You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

- For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctor's hope will be more useful compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about the management of ALT sites for patients who have a similar surgery. This information could help future patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment without being in a study.

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The University of California

What are the costs of taking part in this study?

No additional costs.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Rahul Seth, Dr. Chase Heaton, Dr. P. Daniel Knott, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at 415-476-1814.

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) Dr. Rahul Seth, Dr. Chase Heaton, Dr. P. Daniel Knott at 415-885-7491

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-181

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
Date	Person Obtaining Consent

Date	Witness – Only required if the participant is a non-English speaker