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PROBUPHINE®

(BUPRENORPHINE HCL IMPLANTS) CIII

RISK EVALUATION AND MITIGATION STRATEGY PROGRAM

Agenda

- Introduction
- PROBUPHINE (buprenorphine HCl implants)
  - Indication
  - Patient Selection
- PROBUPHINE REMS Program
  - Goals of REMS Program
  - Mitigating Potential Risks
  - Roles/Responsibilities of Healthcare Providers (HCPs)
  - Certification Process for HCPs
  - Patient Counseling
- PROBUPHINE Insertion and Removal Procedures
  - Step by Step Insertion and Removal Procedures
  - Complications and Risks of Insertion/Removal Procedures

What is the PROBUPHINE REMS

- PROBUPHINE in only available through this REMS Program
  - HCPs Who Prescribe must be certified to place an order PROBUPHINE
  - HCPs Who Inserts/Remove PROBUPHINE must be certified to perform the procedures
  - PROBUPHINE will distributed through a Closed Distribution System ONLY to HCPs Who Precribe PROBPUHINE and either (i) are certified to insert/remove or (ii) make arrangements for a certified HCP Who Inserts/Removes to perform the procedures

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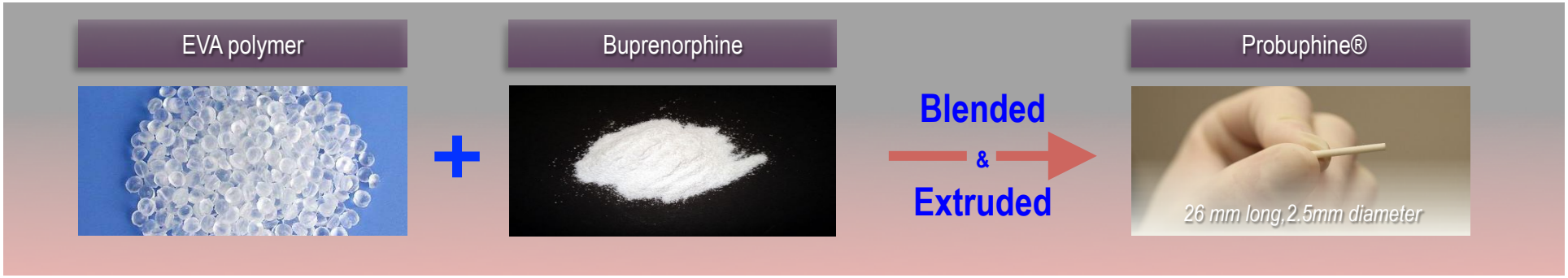
PROBUPHINE®

(Buprenorphine HCl Implants) CIII

PROBUPHINE
(Buprenorphine HCl Implant)

To be updated to align with final PI



- PROBUPHINE is an implantable formulation of buprenophine
- Each implant contains 80 mg of buprenorphine HCl, uniformly distributed throughout the ethylene vinyl acetate co-polymer (EVA) matrix
- 4 PROBUPHINE® implants are inserted subdermally in the upper arm in a simple office procedure and deliver continuous, stable blood levels of buprenorphine for **6 months**
- Must be inserted and removed only by HCPs certified in the REMS Program
- Dosage will be 4 PROBUPHINE implants
- Supplied in a carton containing 4 individually packaged implants and sterile disposable applicator

Indication

To be updated to align with final PI

- PROBUPHINE INDICATION TBD

PROBUPHINE REMS Program

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REMS

- A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure the benefits of a drug outweigh its risks.
- **Braeburn Pharmaceuticals** has worked with the FDA to develop the Probuphine REMS Program to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with the improper implantation and removal of Probuphine and the risks of accidental overdose, misuse and abuse

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Goals of PROBUPHINE REMS

The goal of the PROBUPHINE REMS is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associate with the improper insertion and removal of PROBUPHINE and the risks of accidental overdose, misuse and abuse by:

a. Ensuring that healthcare providers are educated on the following:
   - Proper insertion and removal of PROBUPHINE
   - Risk of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal of PROBUPHINE
   - Risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin

b. Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with improper insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin

PROBUPHINE REMS: Mitigating Potential Risks

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1. Mitigating complications associated with the improper insertion/ removal
   - Education on the risks associated with improper insertion/removal procedures
   - HCPs Who Prescribe will be educated/trained on:
     - Proper and aseptic insertion/removal procedures
     - Appropriate care of the incision
     - Managing complications associated with insertion/removal
     - Referring patients when there are concerns regarding the incision and insertion site
   - HCPs Who Insert/Remove will be educated, trained and demonstrate proficiency on:
     - Proper and aseptic insertion and removal procedures
     - Appropriate care of the incision
     - Managing complications associated with insertion/removal
2. Mitigating the risks of accidental overdose, misuse, and abuse associated with PROBUPHINE if an implant comes out or protrudes from the skin
   - HCPs Who Prescribe must use the Patient Counseling Tool
   - HCPs Who Insert/Remove must provide and counsel patients using the Medication Guide

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HCP Roles/Responsibilities

- HCPs Who Prescribe PROBUPHINE
  - Complete PROBUPHINE REMS Program training and become certified to Prescribe PROBUPHINE
  - Counsel patients using Patient Counseling Tool
  - Document insertion/removal of PROUBHINE using the Insertion/Removal Log and include the log in the patient's chart
  - Need to enroll into PROBUPHINE REMS Program to order PROBUPHINE from the distributor
- HCPs Who Insert/Remove PROBUPHINE
  - Complete PROBUPHINE REMS Program training and become certified to Insert/Remove PROBUPHINE
  - Provide the Medication Guide to patients and counsel patients using the Medication Guide
- HCPs Who Prescribe and Insert/Remove PROBUPHINE
  - Complete PROBUPHINE REMS Program training and become certified to Prescribe and Insert/ Remove PROBUPHINE
  - Counsel patients using Patient Counseling Tool
  - Provide the Medication Guide and review the Medication Guide with patients
  - Document insertion/removal of PROBUPHINE using the Insertion/Removal Log and include the log in the patient's chart
  - Need to enroll into PROBUPHINE REMS Program to order PROBUPHINE from the distributor

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HCP Roles/Responsibilities

- All HCPs must complete REMS training and be certified to:
  - Prescribe PROBUPHINE
  - Insert/Remove PROBUPHINE
  - Both Prescribe and Insert/Remove PROBUPHINE in a dual role

- All HCPs must provide patient education and counseling using:
  - Patient Counseling Tool
  - Medication Guide
  - Both (if one HCP will Prescribe and Insert/Remove PROBUPHINE)

- Prescribing HCP must document insertion/removal using the Insertion/Removal Log and place the log in the patient's chart

HCP Certification Process

- HCPs Who Prescribe PROBUPHINE
  - Didactic and Live Practicum training
  - Pass the Knowledge Assessment Test
  - Complete the “HCP Who Prescribes Enrollment Form”
- HCPs Who Insert/Remove PROBUPHINE
  - Didactic and Live Practicum training
  - Pass the Knowledge Assessment Test
  - Meet the criteria for procedural competency
  - Complete the “HCP who Inserts/Removes Enrollment Form”
- HCPs Who Prescribe and Insert/Remove PROBUPHINE
  - Didactic and Live Practicum training
  - Pass the Knowledge Assessment Test
  - Meet the criteria for procedural competency
  - Complete the “HCP Dual Enrollment Form”

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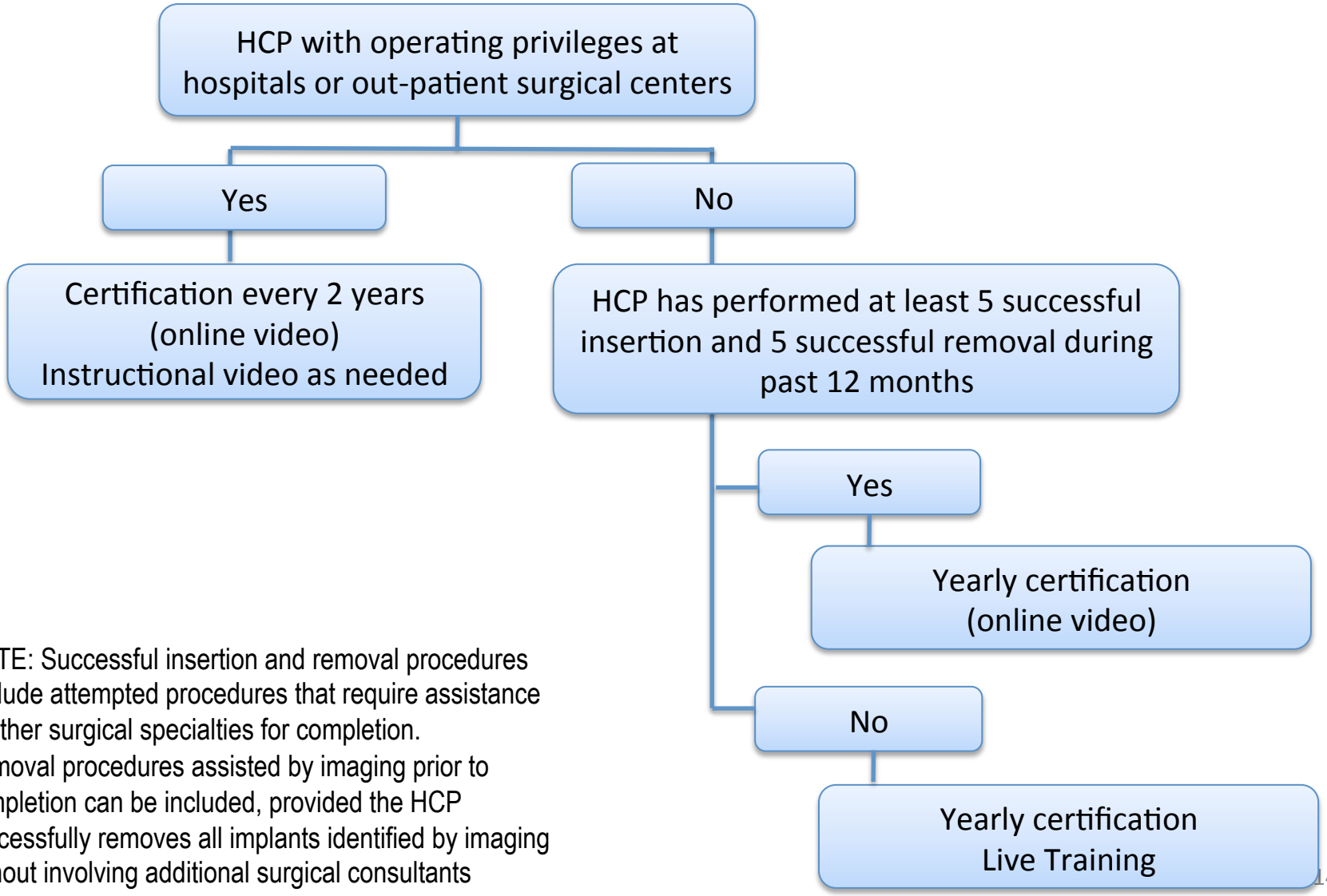
HCP Recertification Process



NOTE: Successful insertion and removal procedures exclude attempted procedures that require assistance of other surgical specialties for completion.
Removal procedures assisted by imaging prior to completion can be included, provided the HCP successfully removes all implants identified by imaging without involving additional surgical consultants

Patient Counseling, Medication Guide, & Care of the Incision

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Patient Counseling and Medication Guide

- All HCPs will provide patient counseling
- Two resources will be utilized for patient counseling:
  - Medication Guide
  - Patient Counseling Tool
- HCPs who Insert/Remove and HCPs who Prescribe and Insert/ Remove will use the Medication Guide to counsel patients prior to insertion procedure
- HCPs who Prescribe and HCPs who Prescribe and Insert/ Remove will counsel patients using the Patient Counseling Tool

Patient Education on Potential Risks: Improper Insertion and Removal of PROBUHINE

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- Possible risks related to improper insertion and removal of PROBUPHINE include:
  - An implant may come out by itself, or an end of the implant may begin to stick out of the skin
  - Injury to nerves or blood vessels could occur
  - Implants may be difficult to locate, if they are inserted too deep or manipulated by the patient, of if the patient has gain significant weight since insertion
  - Special procedures or a referral to a specialist may be needed to remove the implants if they are difficult to locate

Patient Education on Potential Risks: Insertion and Removal Procedures

Last part checked With Med Guide

- Following are some common risks associated with any minor surgical procedure
  - Itching, pain, irritation or redness, swelling, bleeding, or bruising a the insertion site
  - Scarring around the insertion site
  - Infection at the site of the insertion or removal
- Appropriate care of the incision is important to reduce the risk of complications associated with the insertion and removal of PROBUPHINE
- When to call a HCP right away:
  - If the patient no longer is able to feel all four implants
  - If the implants comes out or the end of the implant starts to stick out of the skin
  - If the patient have excessive or worsening itching, pain, irritation or redness, swelling, bleeding, bruising, numbness, or scarring at the insertion site

Patient Education on Potential Risks: Care of the Incision Instructions

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- Patients may return the next day to check the wound
- When the patient comes back:
  - Check for signs of infection: heat, redness, pain, puss,
  - Check for suture complications: knot failure, wound dehiscence
- Explain proper care of the incision to the patient:
  - Keep the wound clean and dry as possible
  - Apply ice pack as needed
  - Remove pressure bandage after 24 hrs
  - Gently wash the wound with soap and water
  - Dry carefully, and apply a small amount of topical antibiotic ointment
  - Replace the adhesive bandage
  - Look for signs and symptoms of infection: Increased pain, swelling, redness, fever, drainage of pus or pus-like material. If these occur, counsel to contact their physician immediately

Patient Education:

Risks of Accidental Overdose, Misuse and Abuse

- There are risks of accidental overdose, misuse and abuse associated with the use of PROBUPHINE, if an implant comes out or the end of the implant starts to stick out of the skin
  - Patients should not try to remove PROBUPHINE implants by themselves
  - If PROBUHINE implants protrude or come out, patients should be instructed to:
    - Wash hands, if the patient touches the implants
    - Cover the area of the insertion site with a clean bandage
    - Do not allow others to touch or use the PROBUPHINE implants, since this could be very dangerous
    - If the PROBUPHINE implants comes out, put them in a plastic bag and bring the implants to the patient's doctor right away.
    - Keep the implants away from others, especially children

PROBUPHINE Insertion and Removal Procedure

PROBUPHINE Kit & Insertion/Removal Kit

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(Insertion/Removal Kits available on request)

PROBUPHINE Kits contain:

- Four PROBUPHINE Implants
- PROBUPHINE Applicator
- Patient ID Card & Patient Chart Sticker
- Instruction for Use Booklet
- Package Insert & Medication Guide

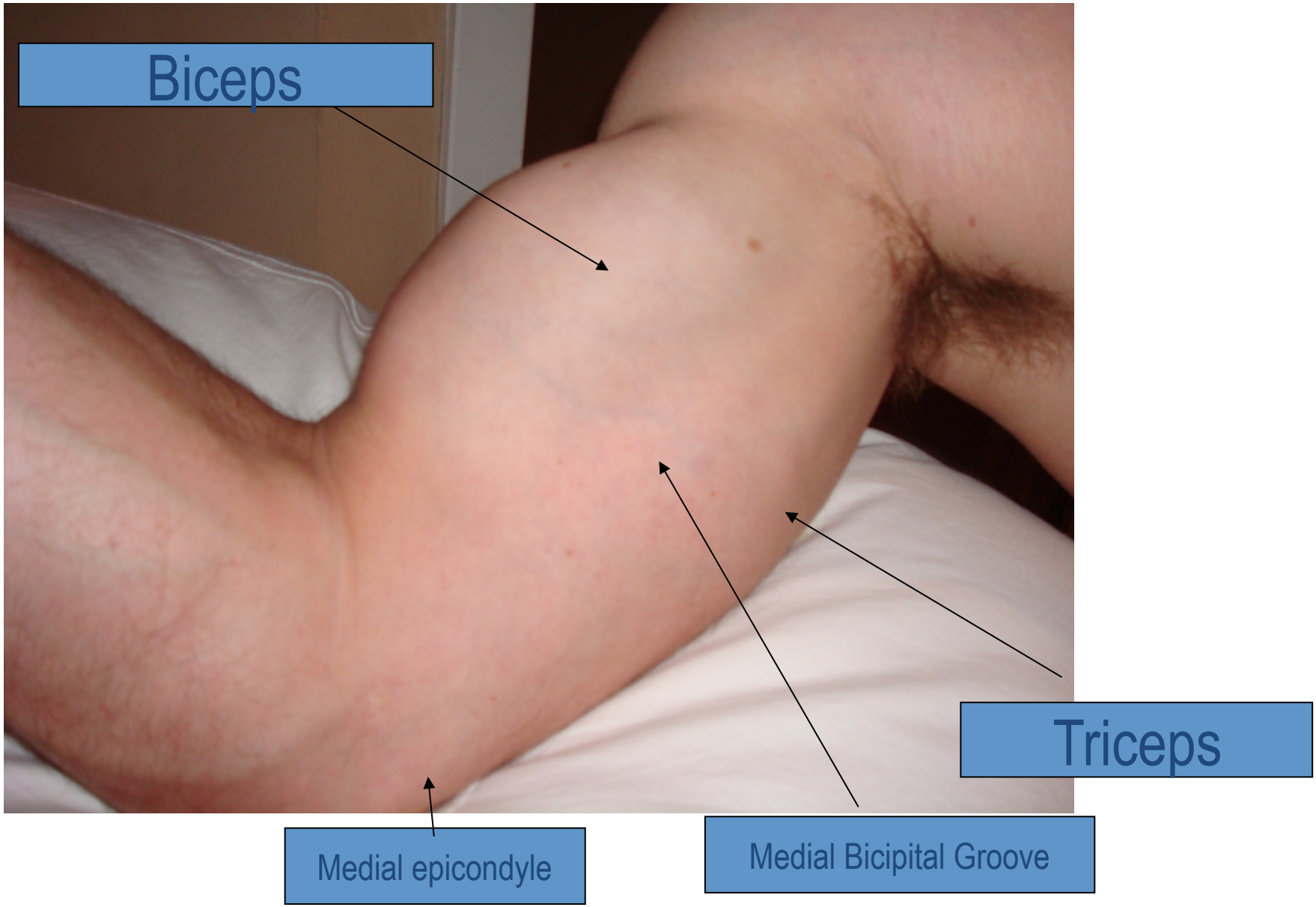
- **Insertion Kits contain:**
  - Surgical drapes, sterile gloves, alcohol prep, ChloraPrep, skin marker
  - 25 g needles, and 5 mL syringe
  - Scalpel with #15 blade
  - Adson single tooth tissue forceps
  - 4 PROBUPHINE implants
  - 1 Single use Applicator
  - Steri-strips, ~~skin~~ liquid adhesive, sterile gauze, adhesive bandage, pressure bandage

- **Removal Kits contain:**
  - Sterile drape, Sterile gloves, ChloraPrep, skin marker
  - 25 g needle, and 5 mL syringe
  - Scalpel with #15 blade
  - Adson single tooth tissue forceps
  - Mosquito forceps
  - X-plant clamps
  - Iris Scissors
  - Needle driver
  - 4-0 Prolene Suture (with FS-2 cutting needle)
  - Sterile gauze, adhesive bandage, pressure bandage

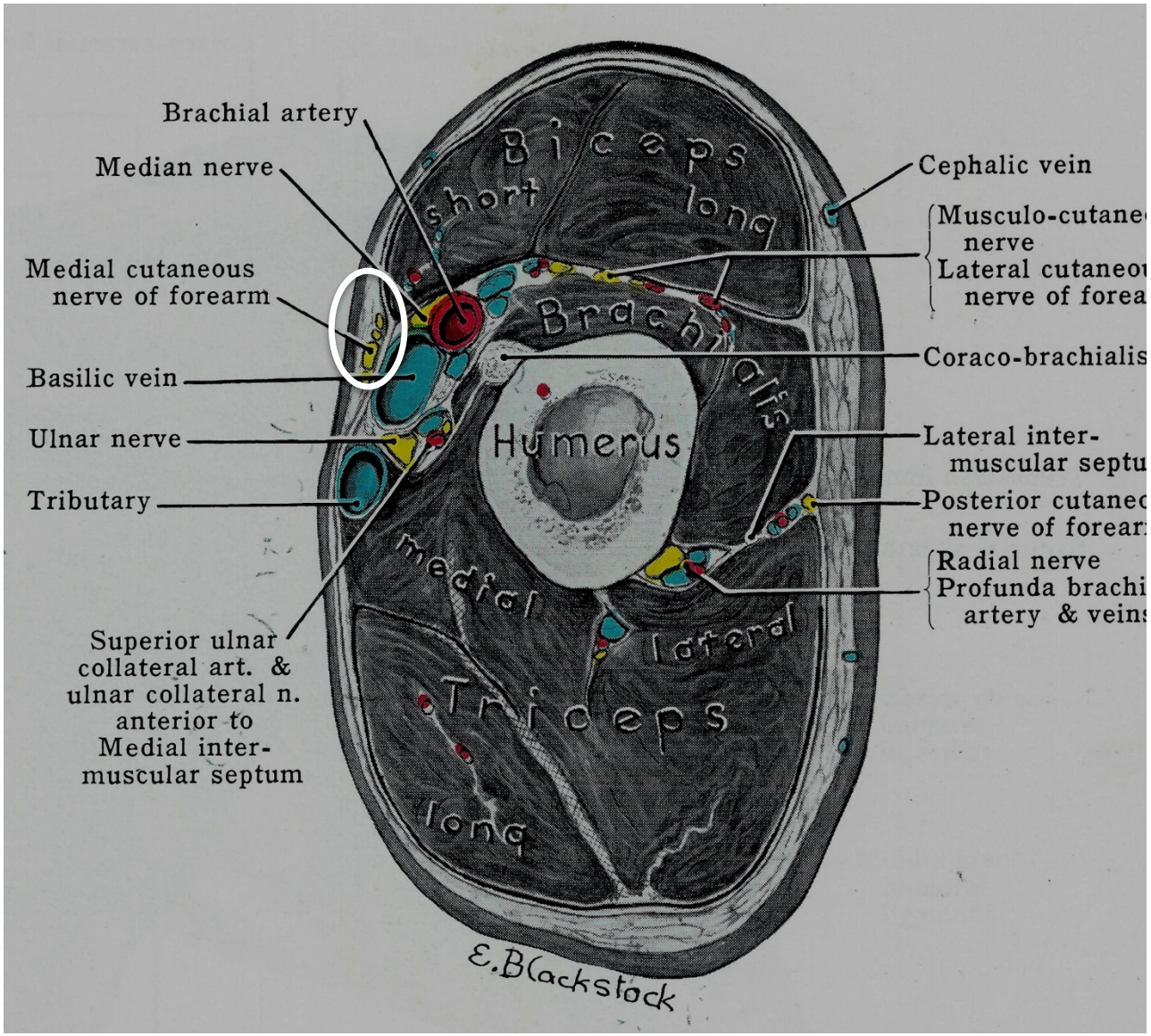
Insertion/Removal Procedure Training Objectives

- Review anatomy of the brachium
- Insertion Procedure
- Implant Localization
- Removal Procedure
- Care of the Incision
- Avoiding Complications & Important potential risks of:
  - Improper Insertion/Removal procedures
  - Accidental overdose, misuse, abuse associated if implant expulsion and protrusion occurs

Brachium


Biceps
Triceps
Medial epicondyle
Medial Bicipital Groove

Brachium Cross Section



Brachium Cutaneous Nerves

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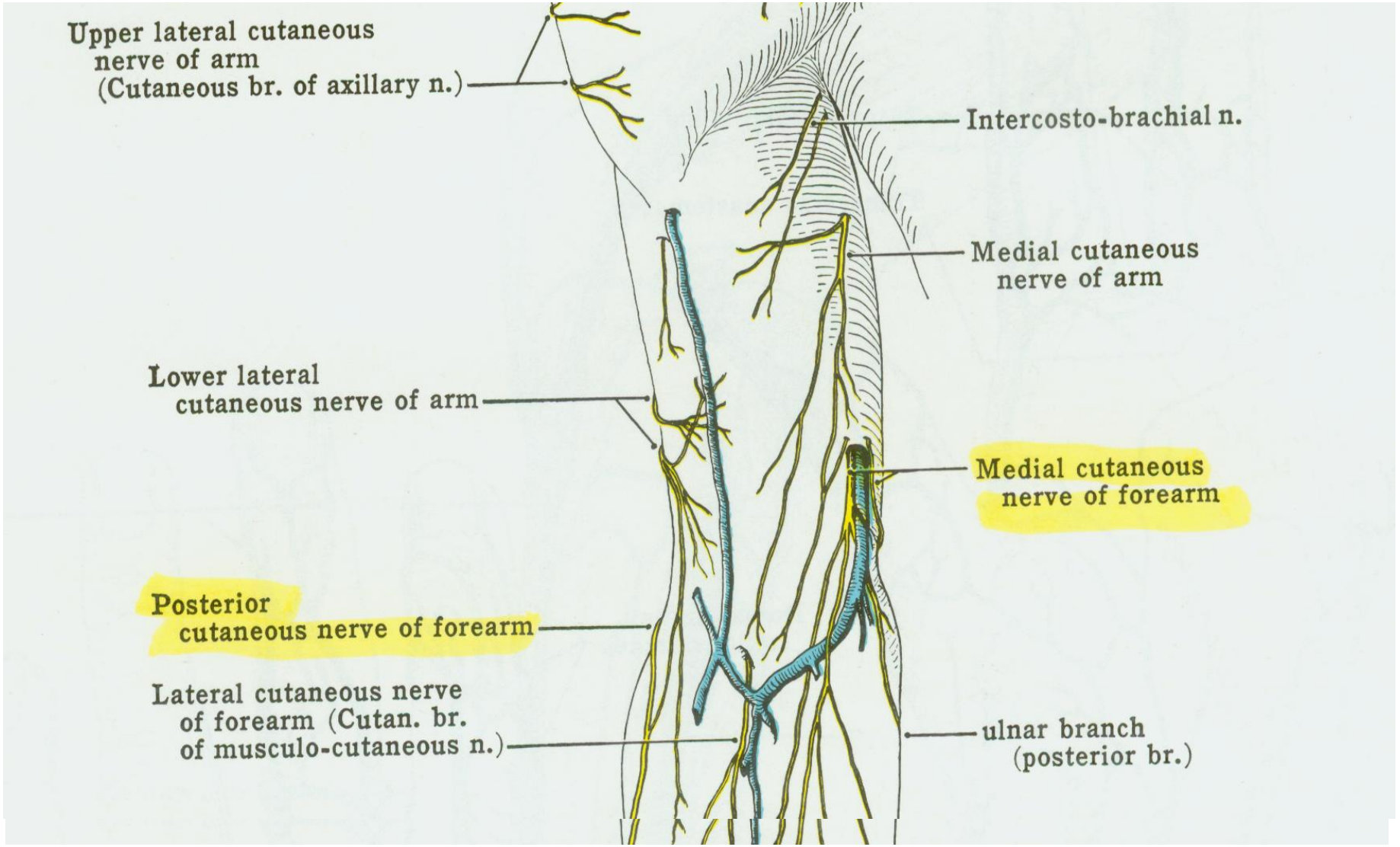
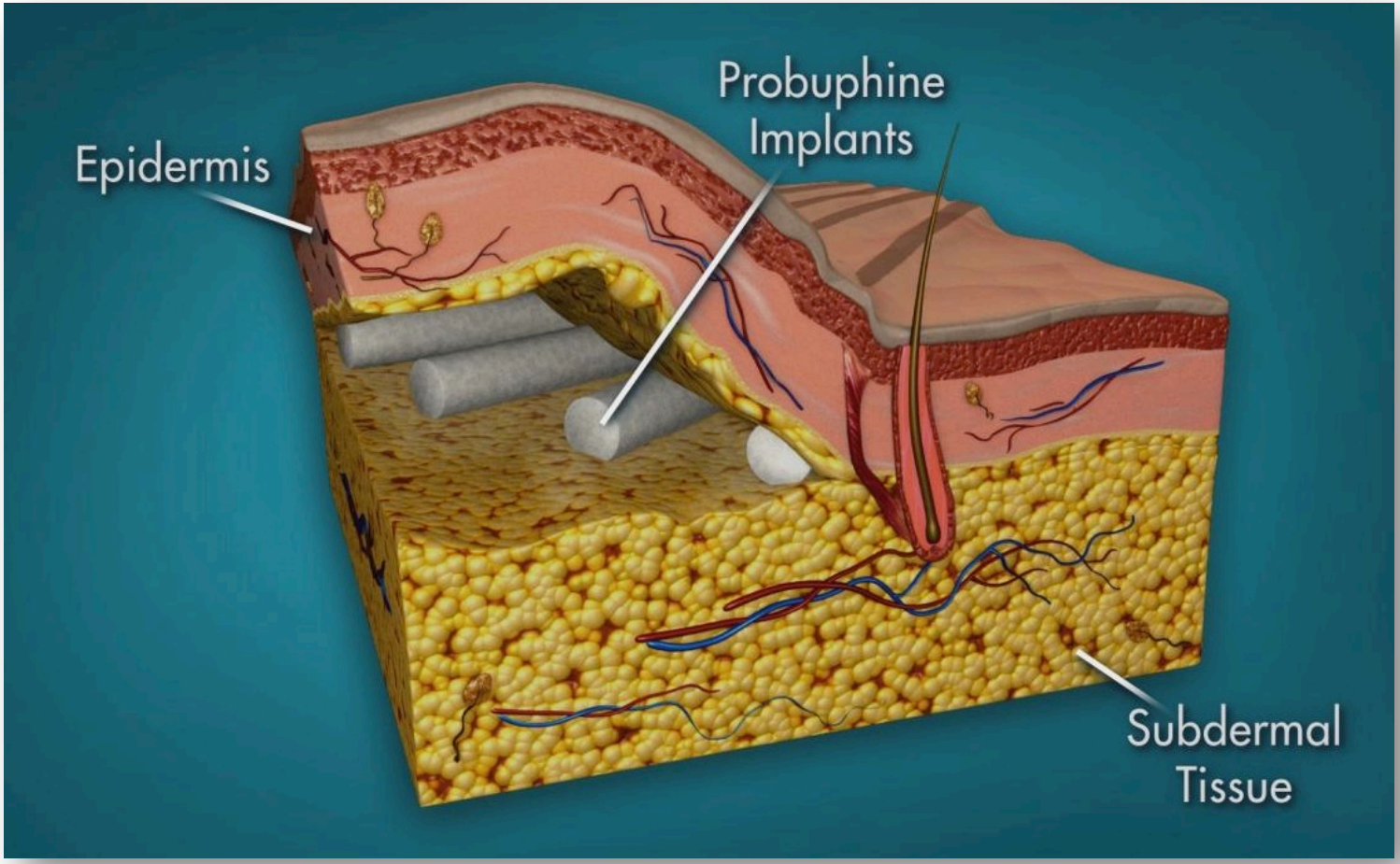


Correct Subdermal Insertion



Careful and correct subdermal insertion is one of the keys to successful placement and will facilitate removal

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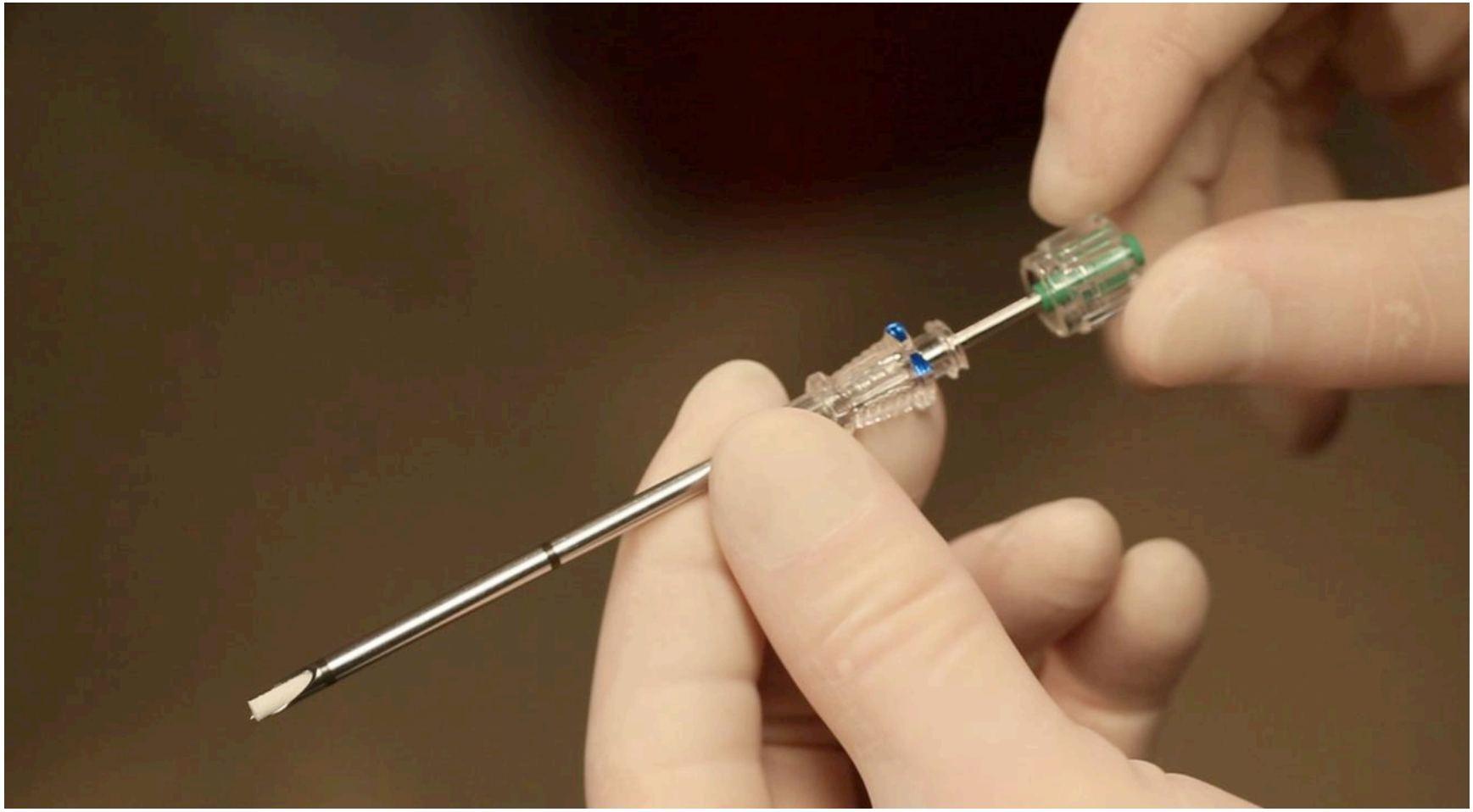
Insertion of PROBUPHINE

PROBUPHINE Insertion Procedure Equipment

Updated SLIDE

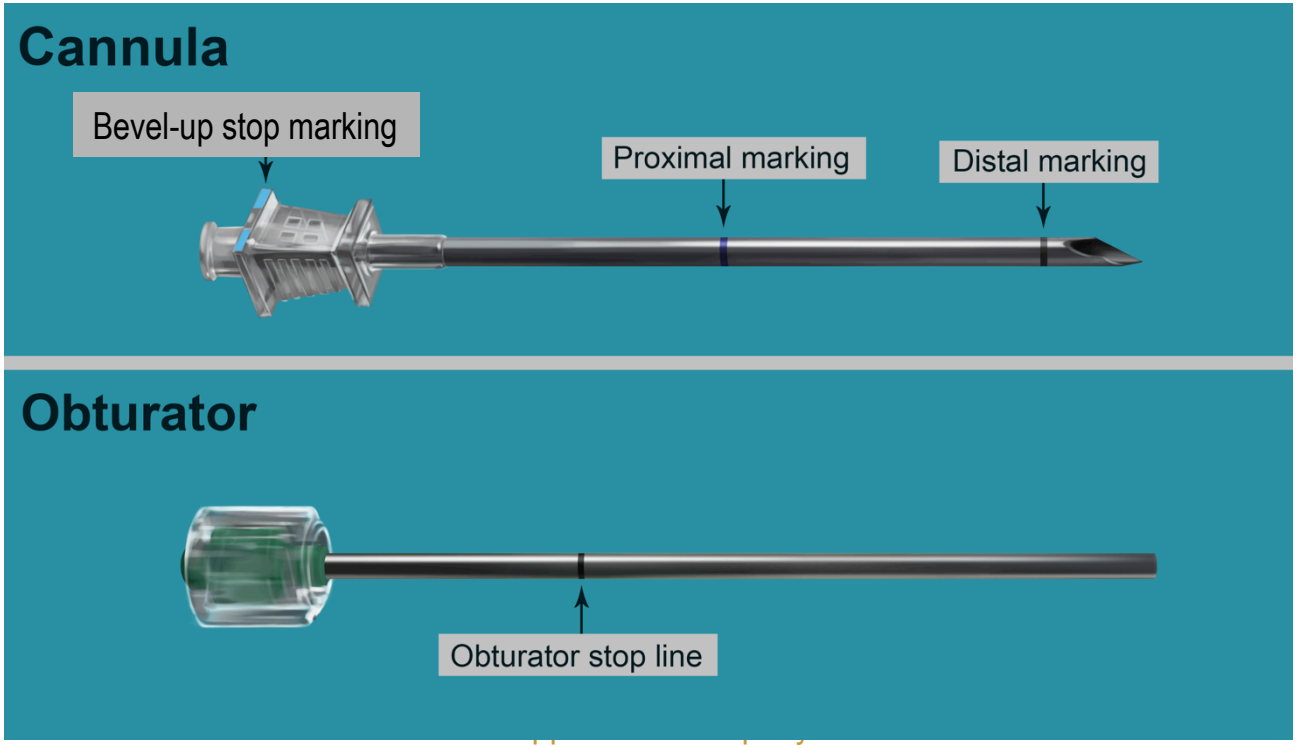
- An examination table for the patient to lie on
- Mayo instrument stand, sterile tray
- Adequate lighting (e.g. headlamp)
- Sterile fenestrated drape
- Latex and talc-free sterile gloves
- EtOH prep
- ChloraPrep
- Marker
- Local anesthetic (1% lidocaine with epinehphrine 1:100,000)
- 5mL syringe with 1.5 inch 25g needle
- Adson single tooth tissue forceps
- #15 blade scalpel
- ¼ inch thin adhesive strip (e.g. Steri-strip skin enclosures)
- 4X4 sterile gauze
- Adhesive bandages
- 3 inch pressure bandages
- Liquid adhesive (e.g. Matisol)
- 4 PROBUPHINE implants
- 1 PROBUPHINE disposable applicator

Insertion Applicator



PROBUPHINE Applicator

Applicator



Updated SLIDE

Insertion Procedure

Step 1. Have the patient lie on his/her back, with his/her non-dominant arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head

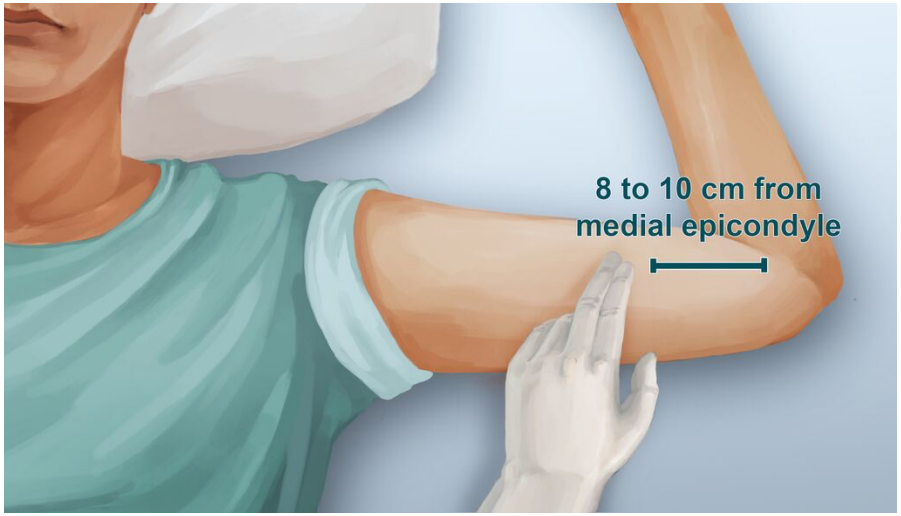
Step 2. Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle. Having the patient flex the biceps muscle may facilitate identification of the site

Updated SLIDE

Insertion Procedure

Step 3. Clean insertion site with alcohol prep pad prior to marking the skin

Step 4. Mark the insertion with a marker. The implants will be inserted through a small 2.5 mm – 3 mm subdermal incision



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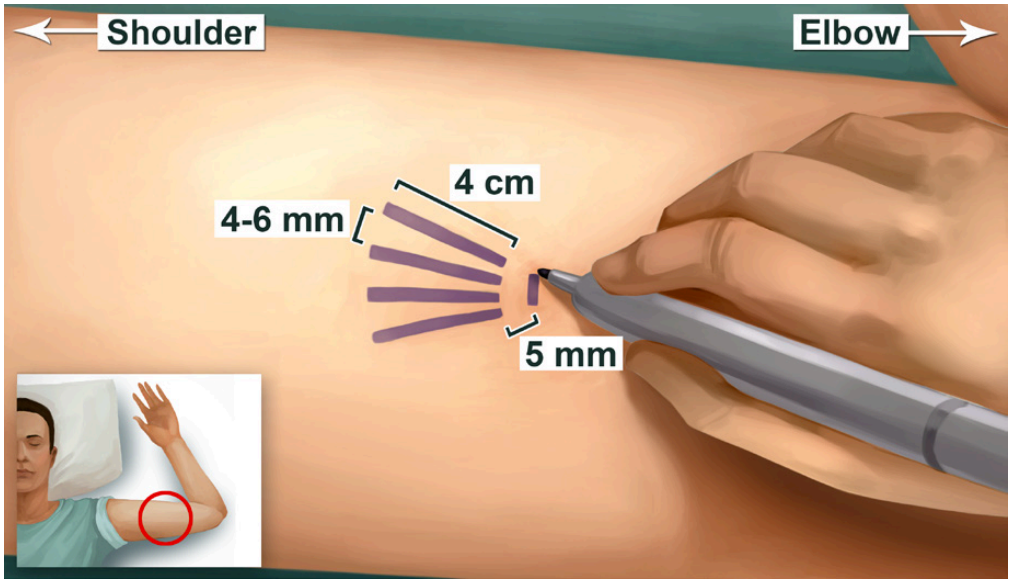
Insertion Procedure

Step 5. Using a marker, mark the channel tracks where each implant will be inserted by drawing 4 lines with each line 4 cm in length.
The implants will be positioned in a close fan shape distribution 4-6 mm apart with the fan opening towards the shoulder.



The closer the implants lie to each other at time of insertion, the more easily they can be removed. There should be at least 5 mm between the incision and the implant when the implant is properly

Updated SLIDE

Insertion Procedure

Step 6. Put on sterile gloves

Step 7. Check applicator function by removing the obturator from the cannula and relocking it

Step 8. Using aseptic technique, place the sterile equipment, PROBUPHINE implants, and the applicator on the sterile field of the mayo instrument stand. One applicator is used to insert all four implants

Step 9. Clean the insertion site with ChloraPrep using gentle repeated back-and-forth strokes for **30 seconds**. When using the triple swabstick applicators, use each swab stick sequentially within the **30 seconds**. Allow the area to air dry for approximately **30 seconds** and do not blot or wipe away

Step 10. Apply the sterile drape to the arm of the patient

Updated SLIDE

Insertion Procedure

Step 11. Anesthetize the insertion area at the incision site and just under the skin along the planned insertion channels using local anesthetic (for example, by injecting 5 mL lidocaine 1% with epinephrine 1:100,000)

Step 12. After determining that anesthesia is adequate and effective, lift the skin with forceps and puncture the skin with a scalpel through the dermis to make a shallow incision that is 2.5 - 3 mm in length

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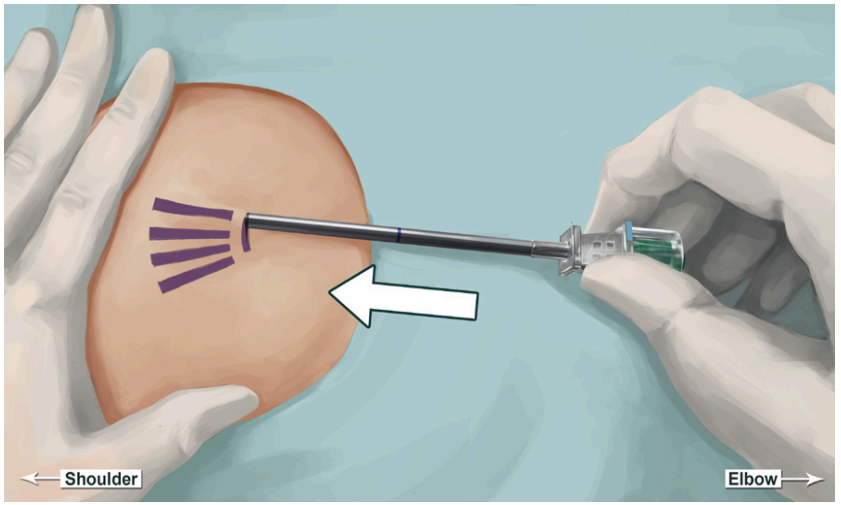
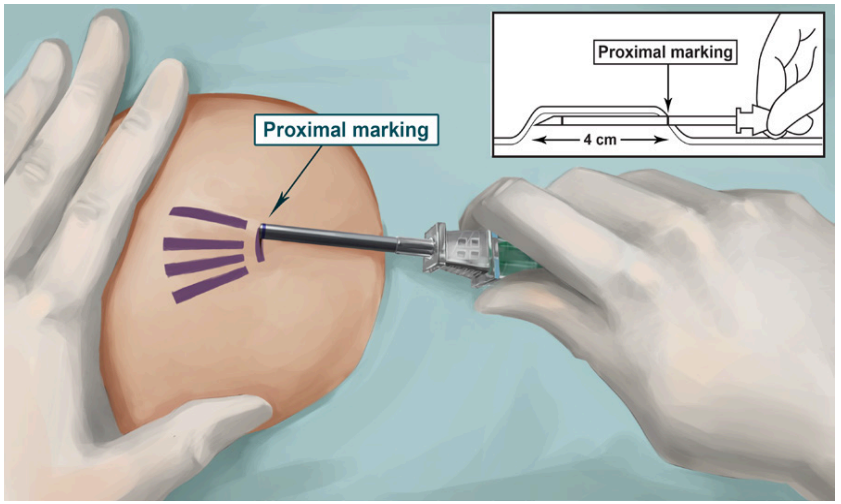
Insertion Procedure

Step 13. Lift the edge of the incision opening with Adson single tooth tissue forceps. While applying counter-traction to the skin, insert only the tip of the cannula at a slight angle (no greater than 20 degrees) in to the subdermal space with the **bevel-up stop marking** on the cannula facing upwards and visible with the obturator locked fully in to the cannula. Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the subdermal connective tissue. While tenting (lifting), gently advance the applicator subdermally along the channel marking on the skin until the **proximal marking** on the cannula just disappears in to the incision





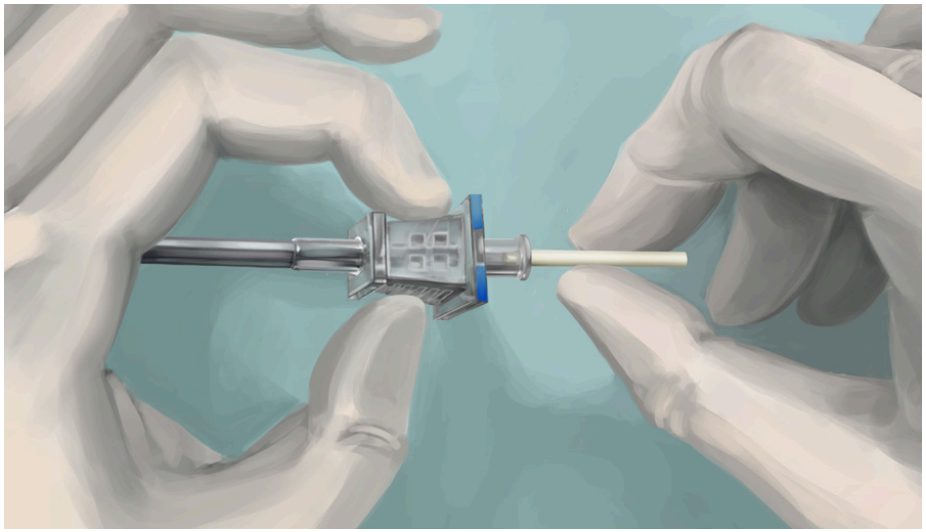
Step 14. Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the subdermal connective tissue

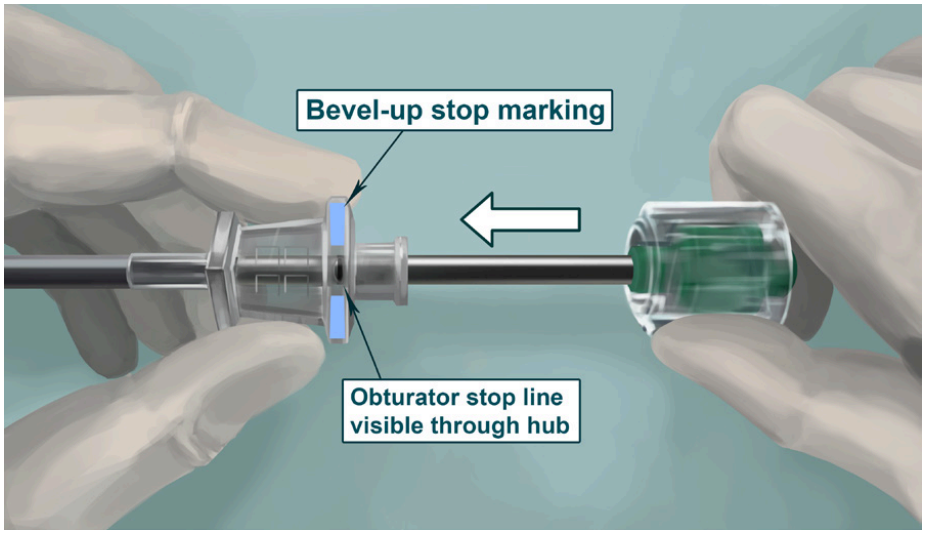
Updated SLIDE

Insertion Procedure

Step 15. While holding the cannula in place, unlock the obturator and remove the obturator

Step 16. Insert one implant into the cannula, re-insert the obturator, and gently push the obturator forward (mild resistance should be felt) until the obturator **stop line** is level with the **bevel-up stop marking**, which indicates the implant is positioned at the tip of the cannula. **Do not force the implant beyond the end of the cannula with the obturator.** There should be at least 5 mm between the incision and the implant when the implant is properly positioned

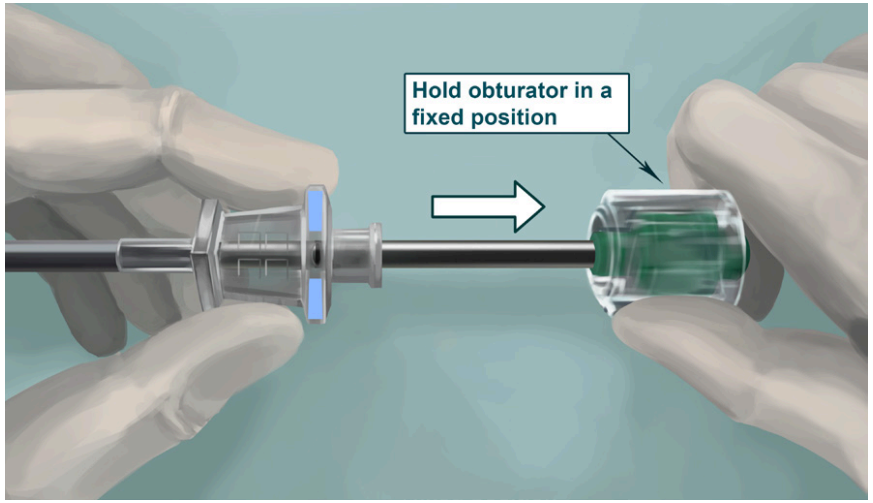




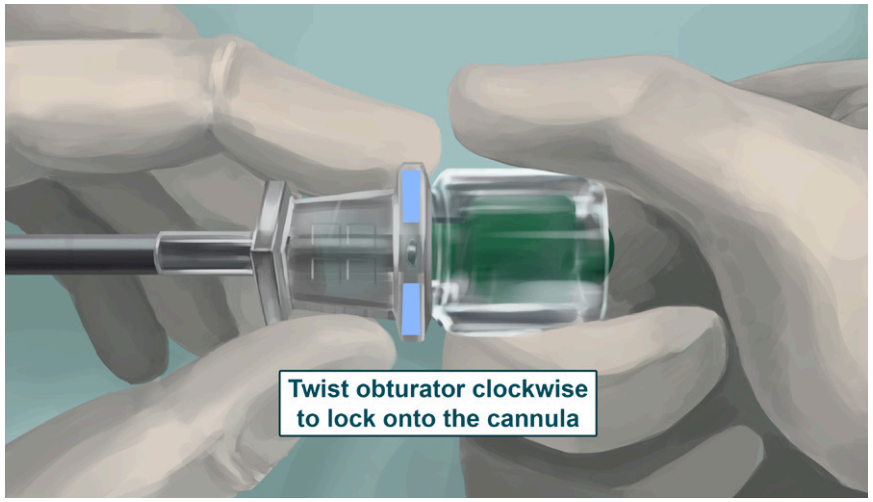
Updated SLIDE

Insertion Procedure

Step 17. While holding the obturator **fixed in place** on the arm, retract the cannula along the obturator, leaving the implant in place. **Note: Do not push the obturator. By holding the obturator fixed in place on the arm and by retracting the cannula, the implant will be left in its correct subdermal position.**



Step 18. Withdraw the cannula until the hub is flush with the obturator, and then **twist the obturator clockwise to lock onto the cannula**. Retract the applicator, **bevel-up**, until the **distal marking** of the cannula is visualized at the incision opening (the sharp tip remaining in the subcutaneous space)

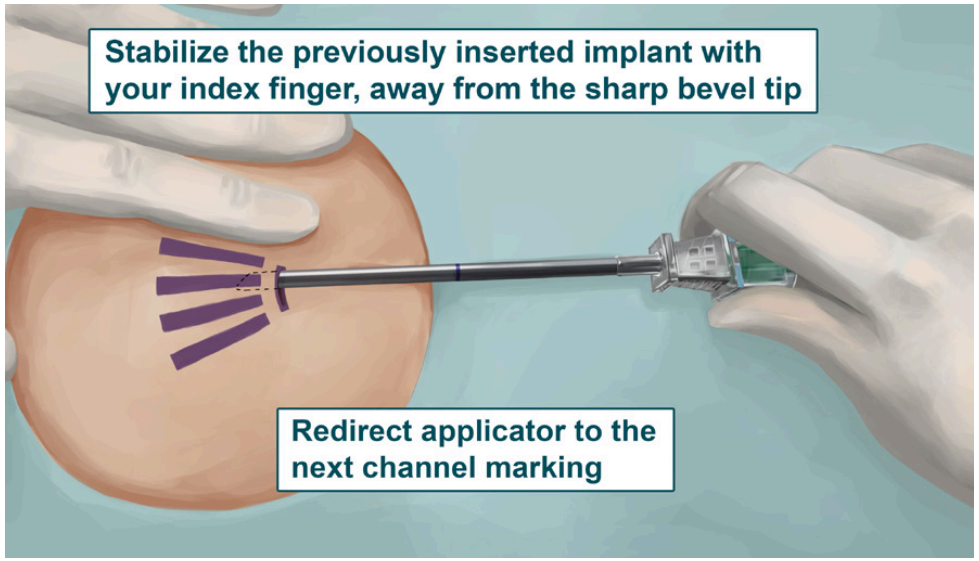


Updated SLIDE

Insertion Procedure

Step 19. Redirect the applicator to the next channel marking **while stabilizing the previously inserted implant, with your index finger, away from the sharp tip**.

Follow steps 13 through 16 for the insertion of the three remaining implants through the same incision, placing implants in a close fan-shaped distribution 4-6 mm apart at the top of the implant. The applicator can now be removed



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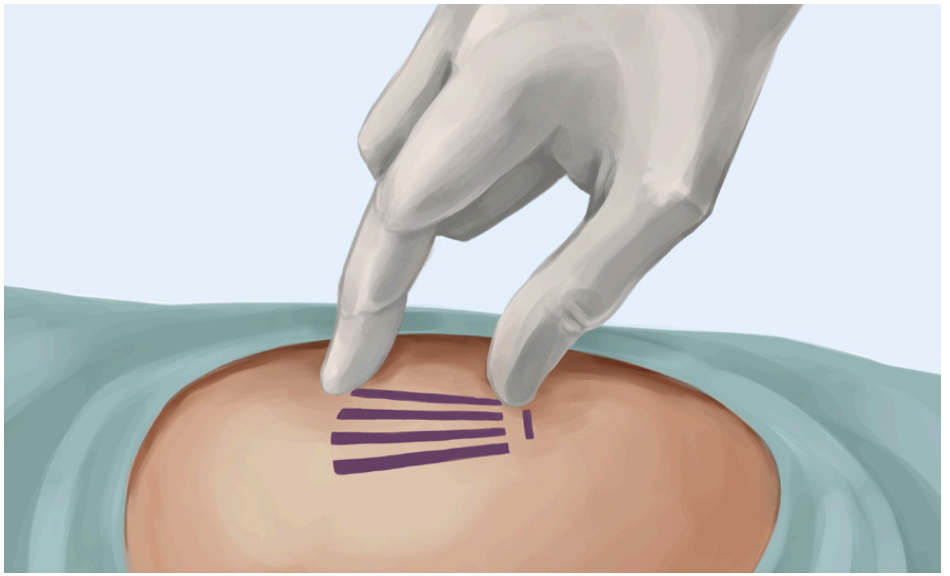
Insertion Procedure

Step 20. Always verify the presence of each implant by palpation in the patient's arm immediately after the insertion. By palpating both ends of the implant, you should be able to confirm the presence of the 26 mm implant.



If you cannot feel each of the four implants, or are in doubt of each of their presence, use other methods to confirm the presence of the implant.

Suitable methods to locate are:

Ultrasound with a high frequency linear array transducer (10MHz or greater), or Magnetic Resonance Imaging (MRI).

Please note that PROBUPHINE implants are not radiopaque and cannot be seen by X-ray or CT scan. If ultrasound or MRI fail, please call 1-844-859-6341.

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Insertion Procedure

Step 21. Apply pressure to the incision site for approximately five minutes if necessary

Step 22. Clean the incision site. Apply liquid adhesive to the skin margins and allow to dry before closing the incision with the 1⁄4 inch thin adhesive strip (butterfly strip) (for example Steri-strip skin closures)

Step 23. Place a small adhesive bandage over the insertion site

Step 24. Apply a pressure bandage with sterile gauze to minimize bruising

Step 25. Complete the PATIENT IDENTIFICATION CARD and give it to the patient to keep. Also, complete the PATIENT CHART LABEL and affix it to the patient medical record. Provide the patient with the Medication Guide and explain proper care of the insertion site

Updated SLIDE

Insertion Procedure

Step 26. **The applicator is for single patient use only**. Dispose the applicator in accordance with the Centers for Disease Control and Prevention guidelines for hazardous waste

Step 27. Complete the PROBUPHINE Patient Distribution Log

PROBUPHINE Applicator Disposal

- **The applicator is for single use only**
- Dispose the applicator in accordance with the Centers of Disease Control and Prevention guidelines for hazardous waste

PROBUPHINE Post-insertion Steps & Medication Guide

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- Explain proper care of the incision
  - Keep the wound clean and dry as possible
  - Apply ice pack/cold compress as needed
  - Remove pressure bandage after 24 hrs
  - Keep adhesive bandage on for 48 hrs
  - Look for signs and symptoms of infection: Increased pain, swelling, redness, fever, drainage of pus or pus-like material. If these occur, instruct to contact their physician immediately
- Provide the patient with the care of the incision sheet and a copy of the medication guide
- Counsel patient using Medication Guide

Live Demonstration by Trainer: Insertion Procedure

Step by Step Insertion Procedure Training

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Localization of PROBUPHINE Implants

PROBUPHINE Localization

- Localization is an essential component of the insertion and removal process
- Always localize:
  - Immediately after insertion
  - Immediately prior to removal
- Localization begins with palpation
- If all PROBUPHINE implants are palpable, localization is complete

Inability to Palpate PROBUPHINE

- **If unable to palpate the implants prior to removal**
  - ***Do not*** **attempt removal or make any incision**
  - **Refer to a radiologist for localization with ultrasound or, if necessary, MRI**
- Attempt removal ***only*** after localization and depth has been confirmed by ultrasound or MRI
  - PROBUPHINE is not radio-opaque and cannot be located by X-ray or CT scan

Removal of PROBUPHINE

PROBUPHINE Removal

- Indications for removal
  - At the end of 6 months of treatment
  - Patient request
  - Medical indication
- Prior to removal carefully read the removal Instructions
- Counsel patients about removal procedure
- **Do not attempt removal until the location of the implants have been verified by palpation or imaging**
- Confirm no allergies to antiseptic and anesthetic
- Prepare aseptic conditions
- Allow 45 minutes for removals

PROBUPHINE Removal Procedure Equipment

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- An examination table for the patient to lie on
- Mayo instrument stand, sterile tray
- Adequate lighting (e.g. headlamp)
- Sterile fenestrated drape
- Latex and talc-free sterile gloves
- EtOH prep
- ChloraPrep
- Marker
- Local anesthetic (1% lidocaine with epinehphrine 1:100,000)
- 5 mL syringe with 1.5 inch 25g needle
- Adson single tooth tissue forceps
- #15 blade scalpel
- Mosquito forceps
- Two X-plant clamps
- Iris Scissors
- Needle driver
- #15 blade scalpel
- 4x4 sterile gauze
- Adhesive bandages
- 3 inch pressure bandages
- Sutures (4-0 Prolene with an FS-2 cutting needle)

Updated SLIDE

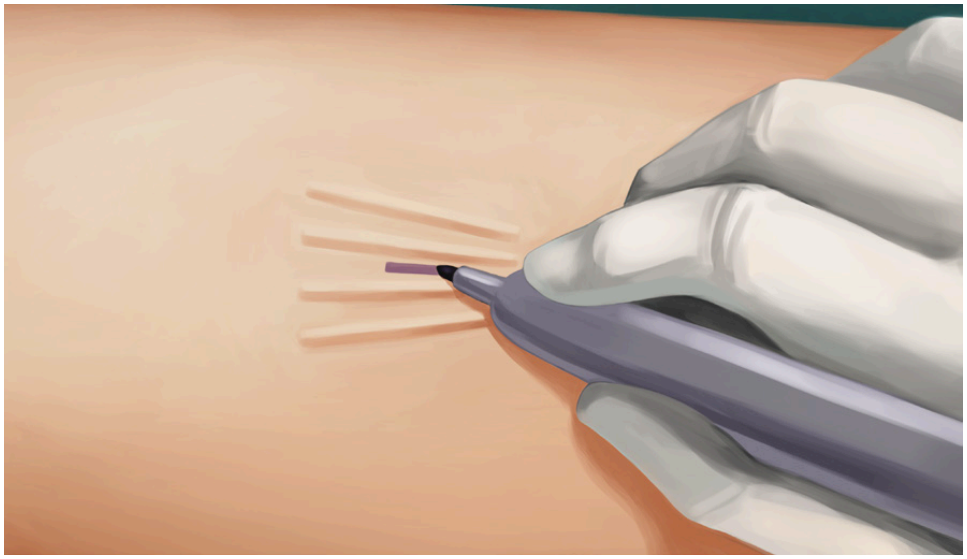
Removal Procedure

Step 1. Have the patient lie on his/her back, with the implant arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head

Step 2. Reconfirm the location of the implants by palpation

Step 3. Clean removal site with alcohol prep pad prior to marking the skin

Step 4. Mark the location of the implants with a marker. In addition, mark the location of the incision, parallel to the axis of the arm, between the second and third implants



Updated SLIDE

Removal Procedure

Step 5. Put on sterile gloves

Step 6. Using the aseptic technique, place the sterile equipment on the sterile field of the mayo instrument stand

Step 7. Clean the removal site with ChloraPrep using gentle repeated back-and-forth strokes for **30 seconds**. When using triple swabstick applicators, use each swabstick sequentially within the **30 seconds**. Allow the area to air dry for approximately **30 seconds** and do not blot or wipe away

Step 8. Apply the sterile drape to the arm of the patient

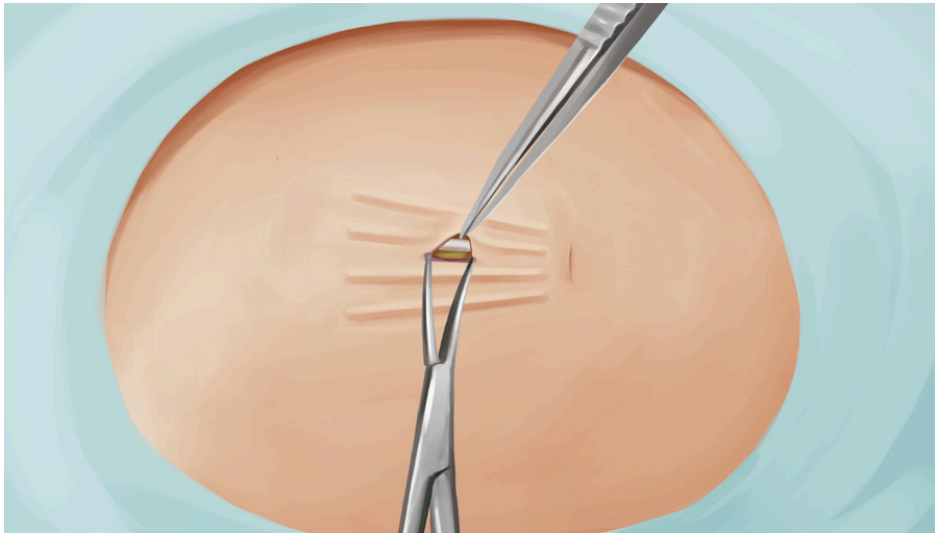
Step 9. Anesthetize the incision site and the subcutaneous space containing the implants (for example, by injecting 5-7 mL lidocaine 1% with epinephrine 1:100,000). **Note: Be sure to inject the local anesthetic just beneath the implants; this will effectively lift the implants toward the skin, facilitating removal of the implants**

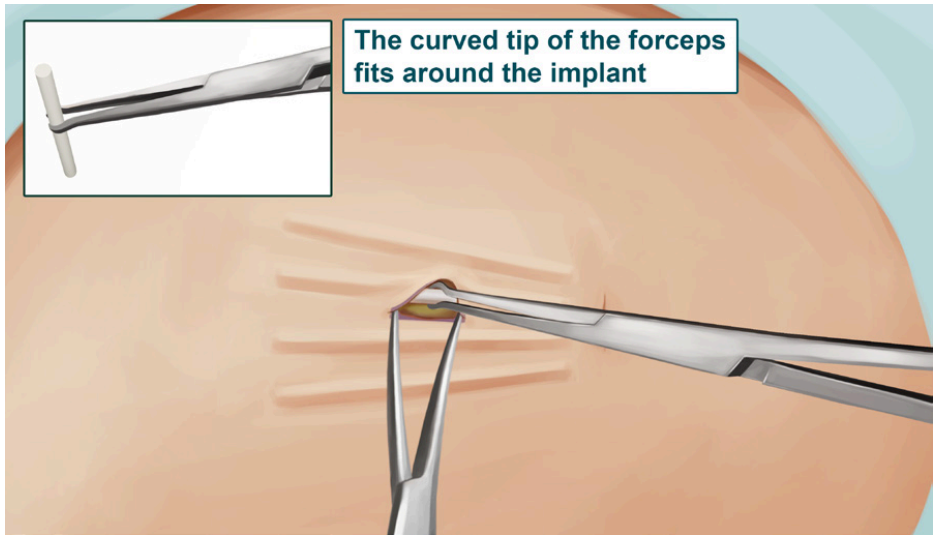
Step 10. After determining that anesthesia is adequate and effective, make a 7-10 mm incision with a scalpel, parallel to the axis arm, between the second and the third implants

Updated SLIDE

Removal Procedure

Step 11. Pick up the skin edge with Adson single tooth tissue forceps and separate the tissues above and below the first visualized implant using an iris scissors or a curved mosquito forceps. Grasp the center of the implant with the X-plant clamp and apply gentle traction. Use the technique of spreading and closing with either the iris scissors or mosquito forceps to separate the fibrous tissue. If the implant is encapsulated use the scalpel to shave the tissue sheath and carefully dissect the tissue around the implant. The implant can then be removed





Updated SLIDE

Removal Procedure

Step 12. Retract the next visible implant toward the incisional opening. You may see tenting of the skin at this point if the surrounding tissue is still adhering to the implant. Maintain gentle traction on the implant while you continue to dissect proximally and distally until the implant is free of all adhering tissue. At this point, you may require the use of your second X-plant clamp to remove the implant. If the implant is encapsulated use the scalpel to shave the tissue sheath and carefully dissect the tissue around the implant. The implant can then be removed

Step 13. After removal of each implant, confirm that the entire implant, which is 26 mm long, has been removed by measuring its length. If a partial implant (less than 26 mm) is removed, the remaining piece should be removed by following the same removal instructions. It is difficult to visually confirm that the entire implant has been removed. Therefore, it is important to measure the implant to ensure the entire implant has been removed

Follow steps 10 through 12 for the removal of the remaining implants through the same incision

Updated SLIDE

Removal Procedure

Step 14. After removal of all four implants, clean the incision site

Step 15. Close the incision with sutures

Step 16. Place an adhesive bandage over the incision

Step 17. Use the sterile gauze and apply gentle pressure for five minutes to the incision site to ensure hemostasis

Step 18. Apply a pressure bandage with sterile gauze to minimize bruising

Step 19. Counsel the patient on proper aseptic wound care. Instruct the patient to apply an ice pack to his/her arm for 40 minutes every two hours for first 24 hours and as needed and to apply a small amount of topical antibiotic ointment after the adhesive bandage is removed.

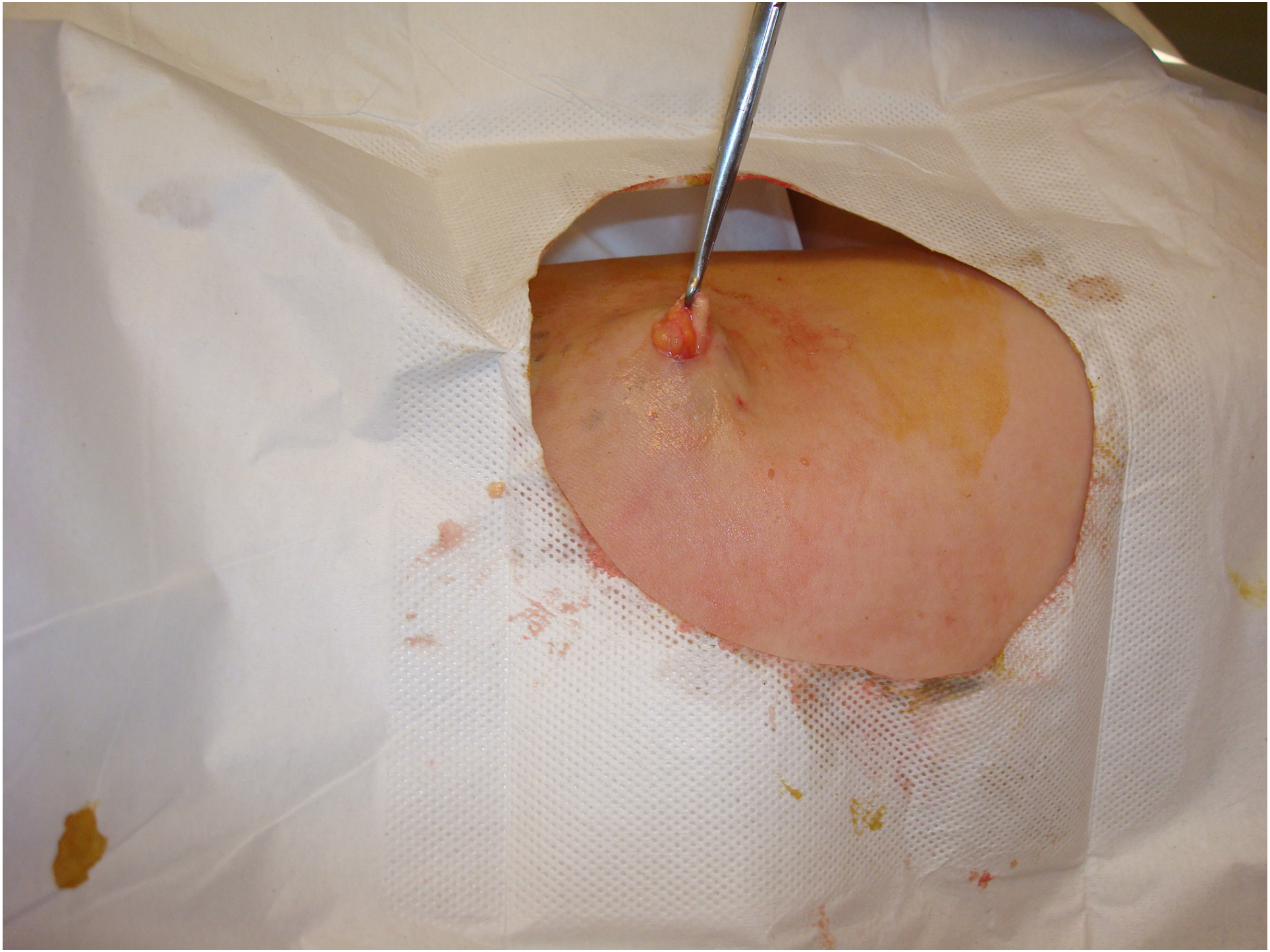
Updated SLIDE

Removal Procedure

Step 20. Schedule an appointment for the sutures to be removed

Step 21. Dispose of PROBUPHINE implants in keeping with local state and federal regulations governing the disposal of pharmaceutical biohazordous waste

Step 22. Complete the PROBUPHINE Distribution Log-Patient (PDL-P)



Care of the Incision
Instruction for Patients at Home

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- When the patient comes back:
  - Check for signs of infection: heat, redness, pain, pus
  - Check for suture complications: knot failure, wound dehiscence
- Explain proper care of the incision to the patient:
  - Keep the wound clean and dry as possible
  - Apply ice pack as needed
  - Remove pressure bandage after 24 hrs
  - Gently wash the wound with soap and water
  - Dry carefully, and apply a small amount of topical antibiotic ointment
  - Replace the adhesive bandage
  - Look for signs and symptoms of infection: Increased pain, swelling, redness, fever, drainage of pus or pus-like material. If these occur, instruct to contact their physician immediately

Complications and Potential Risks of Insertion and Removal Procedures

Updated SLIDE

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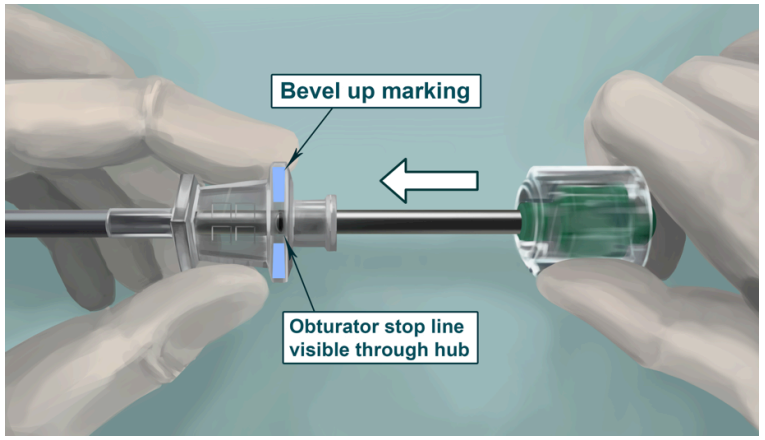
Mitigation of Complications Associated with Improper Insertion/Removal Procedure

- There are risks associated with improper insertion and removal of PROBUPHINE such as:
  - Migration
  - Protrusion
  - Expulsion
  - Nerve damage
- Proper training and education is needed to avoid complications associated with insertion/removal
  - Ensuring proper aseptic insertion/removal procedures
    - NOTE: HCPs Who insert/remove must demonstrate proficiency on proper technique for certification
  - Providing appropriate care of the incision and instructions to patients
  - Appropriate management of complications

Prevention of Deep Insertion

- Insert only the TIP of the applicator, slightly angled no greater than (~ 20°) to prevent neurovascular injury
- Lower the applicator to a horizontal position
- Gently insert, while lifting the skin (tenting), the applicator until the **proximal marking** just disappears into the incision, without using force
- Keep the applicator parallel to the surface of the skin

Prevention of a Fractured/Bent Implant



- During insertion:
  - Avoid pushing the marking the obturator beyond bevel-up marking
  - Withdraw cannula until hub is flush with obturator, twist the obturator clockwise to lock into the cannula
- During removal:
  - Apply gentle traction with X-plant clamp, use an assistant if needed.
  - Do not grasp the implant with hemostat

Prevention of Wound Infection

- Adhere to aseptic technique
- Prep skin with ChloraPrep per product guidelines.
- Instruct patient on proper care of the incision

Updated SLIDE

Mitigating Risk of Accidental Overdose, Misuse, and Abuse, if Implant Explusion or Protrusion Occurs

- Medication in PROBUPHINE can be extracted and then abused in a manner similar to other opioids
- HCPs must make proper patient selection prior to prescribing PROBUPHINE
- HCPs must be properly educated, trained, pass the knowledge assessment, and be certified in the PROBUPHINE REMS Program to prescribe and dispense PROBUPHINE
- PROBUPHINE should not be dispensed to patients for self-administration
- Prior to prescribing PROBUPHINE, prescribers must use the "Patient Counseling Tool" to inform patients about:
  - The risks of accidental overdose, misuse, and abuse
  - When to contact the healthcare provider
- Prior to PROBUPHINE insertion, HCPs Who Insert/Remove must give patients the Medication Guide; and using the Medication Guide, counsel patients on: ~~and counsel pts on Medication Guide on~~
  - The risks of accidental overdose, misuse, and abuse associated with PROBUPHINE if the PROBUPHINE rods come out or protrude from the skin
  - When to contact the healthcare provider

How to Address Potentially Spontaneous Expulsion of Implant

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1. Have the patient retain the implant in plastic bag and return to the office of the implanting physician.
2. Inspect the implant and assure that it is intact. Inspect the remaining in-vivo implants and assure that the correct remaining implants are intact. Document in medical record all findings.
3. Inspect incision site for infection. If infected, treat appropriately and determine if remaining implants need to be removed.
4. Clean expulsion site and close with steri-strips.
5. Insert replacement implant in same arm either medially or laterally to In-Situ implants. Alternatively, replacement implant may be inserted in the contralateral arm.
6. Have patient return in 48-72 hours to inspect insertion site and implants.
7. Dispose of the removed implant per office hazardous waste protocol.

Avoiding Complications: Insertion and Removal

Updated SLIDE

In Summary:

Proper attention to technique and following the instructions will minimize potential problems and complications

Live Demonstration by Trainer: Removal Procedure

Step by Step Removal Procedure Training

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THANK YOU