Title: Assessing the safety and efficacy of a novel subcutaneous implant insertion device on healthy adults

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Title

Assessing the safety and efficacy of the SubQ Assist Implant Insertion Device.

Background

Worldwide, 113 million women have unmet contraceptive needs (Sedgh, Hussain, Bankole, & Singh, 2007). Every year, this unmet need leads to 54 million unintended pregnancies, 26 million abortions, 7 million miscarriages, and 79 thousand maternal and 1.1 million infant deaths (Sedgh et al., 2007). In sub-Saharan Africa, nearly half of married women of reproductive age have expressed the desire to space or limit their pregnancies, but roughly 25% of these women do not use or have access to modern contraception (Pile, Ndede, Ndong, Jacobstein, & Johri, 2007; Tsui, McDonald-Mosley, & Burke, 2010). Within these low- and middle-income countries (LMICs), the major barrier to accessing long-term contraception is the lack of trained healthcare providers, particularly in rural areas where 70% of the population reside ("Population, female," n.d., *World Bank Development Indicators: Agriculture & Rural Development*, 2013). For example, Ethiopia (our initial target market) has only 2.5 physicians per 100,000 residents, a ratio which worsens in rural areas ("Density of physicians," 2009). In LMICs, women typically only have primary access to community healthcare workers (CHWs) who have minimal training and provide a small range of services. Technologies that leverage these readily available CHWs have the highest potential to generate large-scale impact, particularly with respect to providing broad access to long-term contraception.

Subcutaneous contraceptive implants are one of the preferred methods of long-term contraception by the WHO and ministries of health in LMICs. These implants offer between three and five years of protection (allowing women to safely space pregnancies and thereby reduce maternal and infant mortality), are 99.95% efficacious, allow women to return to fertility quickly when removed, requires no daily/monthly effort on the part of the woman, and cause minimal side effects in comparison to other methods. However, availability of contraceptive implants in rural areas of LMICs is limited.

The barrier to increasing access to this form of contraception is the training required to safely administer the implants. Currently, subcutaneous contraceptive implants are inserted free-hand by trained healthcare providers. This requires healthcare providers to precisely thread a large bore needle just beneath the skin along the underside of a woman's arm to deploy the implant (Inc., n.d.; Levine, Sinofsky, & Christ, 2008). If performed correctly, the contraceptive implant is left above the subcutaneous fat layer, just beneath the skin (Figure 1a). However, this freehand method can lead to implants being inserted too deeply, in the fat layer or embedded in the muscle (Figure 1b). In these cases, physicians must use high-frequency ultrasound, MRIs, and surgical techniques to remove these deeply embedded implants, leading to higher costs, participant discomfort, and higher risk of complications/infections (Evans, Holman, & Lindsay, 2005; Gurel et al., 2012; Mansour et al., 2008; Merki-feld, Brekenfeld, Migge, & Keller, 2001; Nelson & Sinow, 1998; Singh, Mansour, & Richardson, 2006). Due to these complications, the World Health Organization recommends that only specially trained providers administer contraceptive implants; significantly limiting their availability in rural areas (World Health Organisation, 2012). Our research team has developed the SubQ Assist, a task-shifting device that facilitates the consistent and accurate administration of contraceptive implants

thereby eliminating complications during removal and allowing community healthcare workers to provide safe access in rural areas.

The SubQ Assist Implant Insertion Device (Figure 1) was co-created by engineering students and clinicians at the University of Michigan (Ann Arbor) and St. Paul's Hospital (Addis Ababa). The initial need for the device was first identified through extensive ethnographic fieldwork performed during August 2013 which included observations and interviews with over 35 healthcare providers (from community health workers to hospital provosts), family planning NGOs, and ministry of health officials. Subsequent designs were then refined through further fieldwork during May 2014, January 2015, and June 2016. In total, we have performed over 200 hours of observations, interviews with more than 110 stakeholders, and have conducted usability tests with 130 healthcare providers in Ethiopia (Mohedas, Daly, & Sienko, 2015). This process has allowed our team to align the design requirements of the SubQ Assist with an established need of the Ethiopian Ministry of Health, meet the requirements of our end-users, and develop our device to meet the regulatory requirements in Ethiopia.

Figure 1: Current design of the SubQ Assist showing the top and bottom views of the device.

The SubQ Assist Implant Insertion Devicewas designed to eliminate the risk of improper insertions regardless of the training level of the healthcare provider. The SubQ Assist is clipped to any standard blood pressure cuff and wrapped around the participant's upper arm. Inflating the cuff to 40 mmHg pushes the skin and subcutaneous tissue into the device's cavity (Figure 2). The guide on the front of the device can then be used to both administer the anesthetic and guide the implant needle just under the skin. In doing so, the SubQ Assist ensures that the implant is administered just beneath the skin and above the subcutaneous fat. This accurate insertion allows for easy removal when the implant needs to be replaced. After deploying the implant, the implant needle, anesthetic needle, and the SubQ Assist are disposed of (fitting the current healthcare environment in rural settings). The efficacy of the SubQ Assist (as measured by the depth accuracy of insertions) has been tested on simulators showing that a minimally trained provider increases accuracy of insertion by ~83% when using the SubQ Assist as compared to traditional free-hand insertion (Mohedas, Sarvestani, et al., 2015). Additionally, the SubQ Assist has been validated through cadaver testing confirming the accuracy of the insertion and the blood pressure insertion methodology.

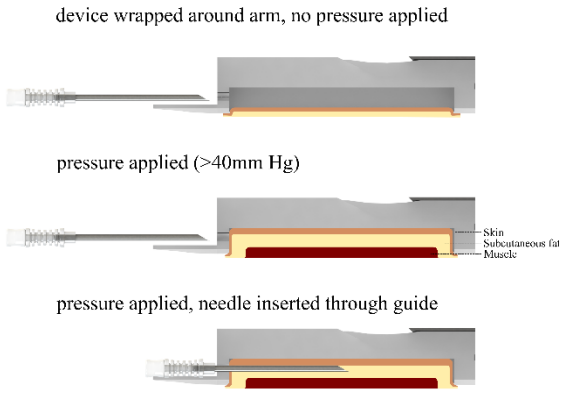


Figure 2: Mechanism demonstrating how the SubQ Assist works and how it ensures accurate administration.

Benefits to Society

Development of the SubQ Assist Implant Insertion Device would dramatically reduce the training barriers to accessing long-acting contraceptive implants. It would enable Ministries of Health in low- and middle-income countries to enable their community healthcare workers (who are readily accessible in rural areas) to administer these implants safely and effectively. This would open up a long-acting contraceptive option to a population of women who are currently underserved and have little access to modern contraception. Based on our analysis of United Nations Data on contraceptive implant use, we estimate that implementation of the SubQ Assist Implant Insertion Device in Ethiopia, Ghana, Kenya, and Uganda would lead to ~750,000 women receiving implants in underserved, rural areas (that currently have limited access. The study below will form the basis for clinical data needed to prove the safety and efficacy of the device.

Research Study

To date, we have performed simulator testing and cadaver testing to assess the efficacy of the SubQ Assist Implant Insertion Device. A trial to assess the safety and efficacy in human subjects is now needed to fully understand how effective the SubQ Assist is with respect to administering contraceptive implants. The study proposed below will allow us to understand whether the SubQ Assist is safe and can effectively place implants just under the skin in the subcutaneous layer.

Objective

The objective of this study is assess the safety and efficacy of the SubQ Assist device.

Specific Aims

SP1: Assess how soft tissue physically behaves when pressurized by the SubQ Assist Implant Insertion Device via a blood pressure cuff.

SP2: Determine the efficacy of the SubQ Assist Implant Insertion Device by measuring the depth of a placebo implant via ultrasound.

SP3: Identify any side effects associated with use of the SubQ Assist as compared to those associated with traditional standard insertion.

Arm 1: Methodology

One factor that may negatively affect the accuracy of the SubQ Assist Implant Insertion Device is the compression of the soft tissue and skin when the blood pressure cuff is inflated around the upper arm. To investigate this, we will be taking Magnetic Resonance Images of the SubQ Assist device inflated around the arm of participants in this arm of the study.

Arm 1: Inclusion Criteria

1. Healthy adults ages 18 to 49
2. Ability to understand study procedure and informed consent document
3. Must be able to have an MRI scan performed

Arm 1: Exclusion Criteria

1. Pregnancy

2. Known silicone allergies
3. Rashes or skin conditions on upper arm
4. Orthopedic or back problems
5. Weight is above the limit for a comfortable MRI scan

Arm 1: MRI Protocol

Below is the step-by-step procedure that will be used. The study will be conducted at the Functional MRI Laboratory within the Biomedical Engineering Department.

1. This study arm will include MRI images of participants while the SubQ Assist Insertion Device is clipped onto an MRI safe blood pressure cuff and inflated on their upper arm. No implant insertions will be conducted within this study arm.
2. During recruitment, a pre-screening questionnaire will be administered to ensure the participant can safely have an MRI. After the pre-screening questionnaire is administered, participants will be sent the full informed consent document and directions for the office visit.
3. Qualified participants will arrive at the BME FMRI laboratory and a study team member will walk participants through the entire procedure.
4. Participants will then review the informed consent with the study team member and have a chance to ask questions. Participants will then sign the informed consent.
5. Participants will then proceed through the pre-screening questionnaire with trained personnel from the BME FMRI center.
6. Once prepared for the scan, participants will have the SubQ Assist Insertion Device clipped onto a MRI safe blood pressure cuff. The cuff will be wrapped around the participants arm and inflated to a pressure less than 100mm Hg.
7. Once inflated, the MRI will be conducted.
8. Once complete, the pressure in the cuff will be released and the participant allowed to take a break.
9. Steps 6 through 8 will be repeated for up to four total pressures in the cuff.
10. After the final scan. The blood pressure cuff will be removed and the participant will be released from the study.

Arm 1: Risk to Participants

The known or expected risks below are ‘rare – infrequent’.

Related to the MRI scan:

1. There is a minor risk of discomfort / anxiety from being in the confined space of the MRI scanner. We will provide pads and blankets to make participants as comfortable as possible. Foam earplugs will also be provided to reduce the loud noises made by the scanner and prevent any hearing damage. Participants will be able to indicate any distress through an intercom system within the MRI scanner. Subjects sometimes report temporary slight dizziness, lightheadedness, or buzzing noises in their ears when leaving the scanner. These potential side effects usually last less than 24 hours.

2. The MRI has the potential to cause “peripheral nerve stimulation” (PNS). PNS can be described as light touching sensation on the skin surface and may cause mild discomfort, but is not harmful. The MRI machine is operated within FDA guidelines so potential for PNS is low.
3. There is a risk that the magnetic resonance image will detect an abnormality indicating a health concern for the participant. However, the scanning procedures used for this study will not be read by a specialist trained to make medical diagnoses from the scan. Therefore, it is unlikely that any abnormality that a participant may currently have will be revealed by the images obtained in this experiment. If any health concerns are discovered, participants will be advised to consult with their physician.
4. Because the strong electromagnetic fields can move metal objects and cause heating, there is a risk that loose objects (jewelry, keys) could be accelerated by the magnetic field and strike the participant, causing injury. There is also a risk that the magnetic fields could disturb a metal fragment in the participant’s body, interfere with an implanted device, such as a pacemaker or neurostimulator, or cause metal (including foil-backed medication patches) on or in the body to heat up, causing harm. The study team will keep the environment around the MRI scanner completely free of loose metal objects that could be moved by the magnetic field, and will make sure that the participant does not have metal on their body that could be affected by the MRI scanner. The pre-screening survey will also ensure that participants have no metal inside their body that would cause harm during the MRI scan.

Related to the SubQ Assist and blood pressure cuff:

1. Discomfort from the blood pressure cuff: the pressure applied to the participant’s arm will be lower than that typically applied during a blood pressure measurement. However, participant’s may find this level of pressure to be uncomfortable. Participants will be asked after each trial their level of discomfort to assess whether they should or should not proceed with the study. Participants will also have the option to relay their discomfort to the study team through the MRI intercom system.
2. Skin irritation: multiple rounds of data collection with the device could result in mild skin irritation. The cuff will be inflated less than five total times to minimize the likelihood the skin irritation is an issue.
3. Bruising from the device: pressure will be applied to the top of the device and transferred to the participant’s arm. This could lead to slight bruising. The study team will work to continually gauge the participant’s level of discomfort and will use longer breaks or stop the study if their discomfort is too great.

Arm 2: Methodology

In order to evaluate the specific aims above, the protocol and data collection templates described below have been developed. In Arm 2, the study team will thoroughly document the insertion of placebo using the SubQ Assist on 50 healthy adults.

Arm 2: Inclusion Criteria

1. Healthy adult subjects ages 18 to 49

2. Ability to understand study procedure and informed consent document

Arm 2: Exclusion Criteria

1. Patients with a history of keloid scarring
2. Pregnancy
3. Any rashes or skin conditions around the insertion site
4. Known silicone allergies
5. Known allergy to lidocaine
6. History of bleeding disorders or abnormal bleeding

Arm 2: Insertion Protocol

Below is the step-by-step procedure that will be used. The study will be conducted at Michigan Clinical Research Unit (MCRU) allowing us to take advantage of clinical services and supplies available.

1. This trial will be conducted on a healthy adult population (50 participants) and a placebo will be used in place of the contraceptive implants. The implant will be made of FDA approved medical grade silicone with properties that match traditional contraceptive implants. The material grade is approved for implantation into the body for less than 24 hours and does not contain any pharmaceutical.
2. A trained physician study member will walk participants through the entire procedure.
3. Participants who agree to participate will then be given the informed consent document to review with the physician. The physician will walk the participants through the document and provide the opportunity for the participant to ask any questions.
4. After signing the informed consent, a researcher will then collect background information on the participant including:
    a. Height
    b. Weight
    c. Arm circumference
    d. Age
5. Placebo implants will then be inserted by a trained physician using the SubQ Assist (See Appendix A for the insertion procedure). The device used in the trial will be 3D printed using biocompatible Class I resins. Each device will be sterilized using an autoclave prior to the procedure. Appendix B Provides more details with respect to the process of manufacturing and sterilizing the SubQ Assist. The placebo implants will be made by Albright Technologies (an ISO 13485 certified producer of medical devices).
6. The physician will use sterile gloves throughout the procedure. Iodine is used to disinfect the area where the SubQ Assist will come into contact with the participant and where the insertion will occur.
7. Lidocaine will be used as local anesthetic along the implant trajectory.
8. After administration the following measurements will be made:
    a. Implant palpability: Can the implant be easily palpated through the skin and, if so, can the entire implant be palpated.

b. Visibility: Can the implant impression be seen when the arm is in a relaxed position?
c. Ultrasound measurement: Ultrasound images of the embedded implant will be taken (which will allow for post-processing to capture the depth of the individual implant).
    i. A research assistant/co-investigator with expertise in ultrasound imaging will administer the ultrasound (Logiq V2 2016 by GE). A 10-15 MHz ultrasound with linear array and 50mm footprint will be used. The ultrasound will be set to superficial focus (<3cm).
        1. Two transverse images will be taken: at the distal and at the proximal ends of the implant.
        2. A third ultrasound image will be taken in the longitudinal direction.
d. Bruising/Bleeding: Notes will be taken on whether any bruising/bleeding is occurring and, if so, how much. Sterile gauze will be used to assess the amount of blood loss (comparing pre- and post-procedure gauze weight to assess amount of blood loss).
e. Photograph: A close-up photo (using Sony DSC-RX100) of the insertion sight will be taken to document the insertion and the insertion site. This will also be used to assess bruising. The photograph will not be identifiable (upper arm only).
f. A case report will be created by the physician to assess the ease of use of the SubQ Assist and to make note of any issues with insertion. The physician administering the implant will address the following in the report:
    i. Did you encounter any issues with the following steps in the insertion process?
        1. Clipping the SubQ Assist onto the blood pressure cuff and wrapping it around the patients' arm?
        2. Inflating the cuff to the appropriate pressure?
        3. Administering the lidocaine?
        4. Inserting the trocar?
        5. Inserting the implant?
        6. Removing the SubQ Assist?

9. Once all measurements are completed, the physician will remove the placebo implant through the original incision made by the implant trocar used. Removing implants through this incision will minimize scarring for the participant. In some cases, a slightly large incision will be required in order to remove the implant (up to 3mm in length) and will be made via a scalpel.
    a. More anesthetic may be applied if necessary during removal based on the following scenarios:
        i. Original dose of lidocaine wears off
        ii. Original dose of lidocaine was too small for removal
        iii. Implant removal is complicated and requires larger inceision
10. After removal, the implants will be measured and photographed (participant not in photograph) to ensure the implant removal was complete.
11. When implant removal is confirmed, a steristrip will be used to protect the incision from infection and facilitate healing.
12. Participants will be given an instructions on how to care for the incision and check for infection issues. The following points will be explained to participants:

a. Only touch the steristrip with clean, washed hands.
b. Keep the steristrip on for 3 days (until the wound has healed over) to prevent dirt and bacteria from reach incision.
c. Keep the incision site dry.
d. Contact the research team or your doctor if you see any of the following signs of infection: redness, oozing, bleeding, inflamed, increasing pain/itchiness, other signs of discomfort in the area of your incision.

Arm 2: Follow-up Check-in (7 days)

1. Participants will be called or emailed (depending on their preference) one week after the insertion procedure to assess any pain or discomfort associated with the insertion protocol.
2. The questions outline in Appendix C will be asked of all participants.
3. Any adverse events will be recorded

Arm 2: Follow-up Visit Protocol (3 weeks ± 1 week)

1. Participants will return for a follow-up visit three weeks after the insertion procedure (± 1 week).
2. During this visit, the incision will be checked for safe healing and infection. Photographs will again be taken of the insertion site to assess potential bruising. Photographs will not be identifiable (consist of upper arm only). Any adverse events will be recorded.

Arm 2: Placebo Implants

The placebo implants used in this study will be manufactured by Albright Technologies Inc (https://albrightsilicone.com). The placebo implant is made to the same specifications as the contraceptive implants with respect to both geometry and material characteristics. The implants are made from short-term implantable silicone which is a grade of silicone that can be implanted in the body for 29 days or less. Manufacturing will be done in a class ISO 7 compliant controlled environment room. Parts will be sterilized and packaged sterile allowing the research team to use a disposable sterile implants for each research participant.

Arm 2: Risks to Participants

The participants in this study will be healthy adults [18-49 years of age]. They will receive a placebo implant (using the SubQ Assist), additional measurements, implant removal, a follow-up check-in, and a follow-up visit.

Participants in this study will be receiving placebo implants. There is no anticipated risk of a decrease in cognitive function during the study and participants will be allowed to withdraw from the study at any time. There is a highly unlikely risk of a reaction to the lidocaine local anesthetic that could occur. A strong reaction would result in the participant being prematurely withdrawn from the study. To minimize this risk, participants will be asked about any prior reactions to anesthesia they may have had in the past during recruitment. Placebo implants will be made of implantable grade silicon (See Appendix D). We will therefore ask participants about potential silicone allergies prior to enrollment in the study. Study

members will monitor participants during the study to assess whether participation in the study needs to end prematurely.

Arm 1: Data Analysis

MRI scans will be taken at multiple pressures and with a diversity of subjects (with respect to their BMI and arm circumference). MRI scans will allow us to evaluate the level of compression of the muscle, subcutaneous fat, and skin when the SubQ Assist Implant Insertion device is pressed again the participant's upper arm when the blood pressure cuff is inflated at various pressures.

Arm 2: Data Analysis

Data collected will include a range of measurements. The key data will be derived from the ultrasound images, namely: distal end depth (mm), proximal end depth (mm), implant depth angle (degrees), and average implant depth (mm). We will assess the depth of implants embedded using the SubQ Assist procedure and comparing this with the data currently available in the literature. We will be looking to assess if there is any difference between the implant depth measurements obtained in this study and the recommended depth of implant by the manufacture and those measurements found in the literature.

Adverse Events

Adverse events will be recorded from the time of consent until the final visit. Adverse events that are observed by the investigator or reported by the subject should be recorded on the CRFs. For all adverse events and complications, a description of the event, date first observed, any action taken, and ultimate outcome will be recorded.

For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the causal relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes.

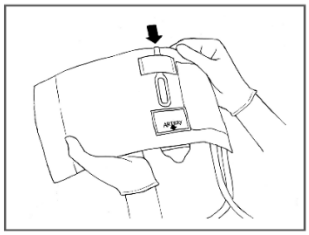
All adverse events and complications should be documented on the CRFs and tabulated for reporting as required according to the FDA and IRB reporting guidelines.

Appendix A

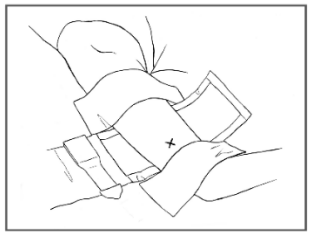
Below we have a detailed discussion of how the SubQ Assist Implant Insertion Device is used to insert the placebo implants:

1. A sterile drape is first draped underneath the upper arm of the participant and a sterile field is created.
2. An insertion mark is made at 6-8cm above the epicondyle.
3. Iodine is used to disinfect the area where the SubQ Assist will come into contact with the participant and where the insertion will occur.
4. The SubQ Assist is removed from its sterile packaging and clipped onto the blood pressure cuff (Step 1 below).
5. The blood pressure cuff is wrapped around the participant's upper arm aligning the device with the insertion site mark (Step 2 below).
6. Once secured, the blood pressure cuff is inflated to ~40mm Hg (Step 3 below). This pushes the skin and subcutaneous tissue into the cavity on the underside of the SubQ Assist.
7. The lidocaine is then inserted through the guide on the front of the device; placing the local anesthetic along the implant trajectory.
8. The cuff is deflated while the lidocaine takes effect.
9. The cuff is re-inflated after a two minute waiting period to ~40mm Hg.
10. The implant trocar is removed from its sterile packaging and inserted through the guide of the SubQ Assist (Step 4 below).
11. The plunger is removed and the sterile placebo implant is removed from its packaging and inserted into the trocar. The plunger is inserted until resistance is felt, the trocar is then pulled back until it touches the plunger.
12. The trocar is rotated to insert an implant in the second directions.
13. The trocar is removed completely, the cuff is deflated and removed from the patients arm.
14. The insertion site is cleaned and a steristrip is applied.

Step 1



Step 2



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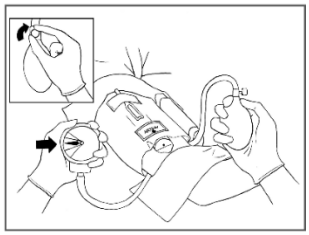

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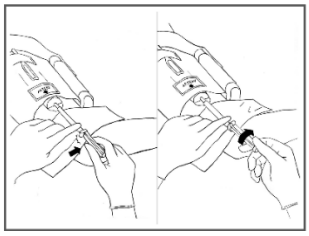

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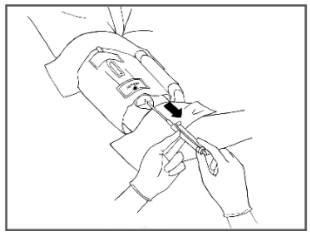

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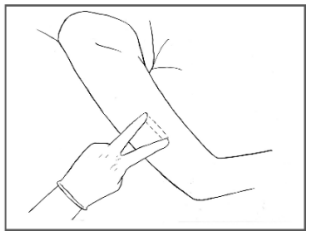

Appendix B

The 3D printed prototypes used in this study will be made using a Formlabs Form 2 printer (https://formlabs.com/3d-printers/form-2/). This printer allows us to manufacture highly accurate (resolution levels of 25 microns) prototypes that will be dimensionally equivalent to the device that would eventually be produced using injection molding and have similar material properties to common biocompatible plastics used within the medical industry. As the SubQ Assist functions almost exclusively based on its geometry and physical characteristics, we believe that the 3D printed devices we are able to produce provide a sufficient similarity to what would be produced at scale during injection molding.

The devices produced will be made from a specific resin used in the 3D printer that is an autoclavable, Class 1 biocompatible resin. This has been extensively used to create surgical guides within dentistry. The ability to autoclave the material (without dimensional deformation) will allow us to create sterile, ready to use devices that minimize the risk of injections occurring at the insertion site.

The material is certified and in compliance with the following standards:

- EN-ISO 10993-1:2009/AC:2010: non-mutagenic, non-cytotoxic, not induce any erythema or edema reactions, not a sensitizer, not cause systemic toxicity
- EN-ISO 20795-1:2013 (Dentistry – Base Polymers – Part 1: Denture Base Polymers)
- EN-ISO 7405:2009/A1:2013 (Dentistry – Evaluation of biocompatibility of medical devices used in dentistry)
- EN-ISO 10993-1:2009/AC:2010 (Biological evaluation of medical devices)

Appendix C

Arm 2: Follow-up phone call / questionnaire:

1. On a scale of 1 to 10, what pain do you currently feel in your upper arm?
2. Is there any bruising on your upper arm?
3. Has there been any fluid draining from the incision?
4. Has there been any redness or swelling of the insertion site?
5. Has there been any bleeding from the insertion site?