Needle-free delivery of intralesional triamcinolone for pediatric alopecia areata: a pilot study of patient tolerability

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Objectives

- **Primary Objectives**
    - Validate patient tolerability of needle-free delivery of intralesional triamcinolone using patient-reported outcome measures.
- **Secondary Objectives**
    - Validate efficacy of needle-free delivery of intralesional triamcinolone for pediatric alopecia areata.
    - Assess the impact of needle-free delivery of intralesional triamcinolone on quality of life for pediatric alopecia areata.

Background

Alopecia areata (AA) is a significant medical condition that causes emotional and psychosocial distress as well as reductions in quality of life, especially in the pediatric population [Aldhouse et al 2020; Mostaghimi 2021; Christensen et al 2017]. When limited and patchy, an estimated 80% of those affected will see spontaneous recovery; however, this disease is characterized by frequent remittances and relapses and may progress to more severe disease – alopecia totalis or alopecia universalis (Ito 2012; Barton 2021). Currently, there are no Food and Drug Administration- (FDA) approved treatments for pediatric alopecia areata, and there is a paucity of well-designed, randomized-controlled clinical trials (Meah et al 2020; Barton et al. 2021). Current recommendations, however, support the use of intralesional triamcinolone acetonide (ILTA) in adults (Meah et al 2020, Yee et al 2019), and pediatric patients (Barton et al. 2021; Fernando et al. 2020; Wang et al. 2012).

The use of ILTA in the pediatric population is often limited due to fear of injections and pain [Hordinsky 2015]. A 2002 chart review by Tan et al. demonstrated >50% improvement in 65% of pediatric patients at 12 weeks with use of ILTA, but >10% of patients dropped out of the study due to pain (Tan et al 2002). Current methods for pain mitigation include small gauge needles, cold sprays, distraction, and topical anesthetics, each with their own limitations (Want et al. 2012). Controlling pain is important as it can result in several physiological, psychological, and emotional consequences such as hypoxemia, vasovagal reaction, tachycardia, life-long needle phobia, fear of other procedures, higher levels of pain during other procedures, and possible avoidance of the healthcare system as adults (Ballard et al 2018; Birnie et al 2018). Given limited treatment options for pediatric patients with AA, ameliorating the fear and pain associated with needle-based ILTA is preferable, and the Med-Jet injector may be a device that can do just that. If well-tolerated, well-designed, randomized clinical trials may be feasible in the pediatric population.

The Med-Jet-MBX needle-free injector (Med-Jet) is a novel, needle-free drug-delivery system, which we believe may be a solution to the pain and fear associated with needles. It uses regulated compressed air as a power source to accelerate an injectable fluid through a 0.005” orifice (6x smaller than a 30G needle) to penetrate the skin and deliver medication to a specific anatomical region (MedJet) The drug-delivery device is highly configurable allowing adjustable depth and volume parameters (MedJet). In addition, the high-performance design allows for triggering multiple injection sites rapidly which is practical when needing to treat large surface areas (MedJet).

Inclusion and Exclusion Criteria

Inclusion Criteria			
	Subjects must meet all of the following criteria to be eligible for this study:	Yes	No
1	6-17 years of age.		
2	Diagnosed with alopecia areata by either: • A board-certified dermatologist, OR • Dermatology Nurse Practitioner, OR • Skin punch biopsy		
3	Patient has at least 2 alopecic patches each measuring at least 2 cm^2 and are… • Located on contralateral body sites **OR** • Within the same body site but separated by ≥ 1 cm		
4	Patient is a candidate for intralesional triamcinolone.		
4	Patient able to give informed assent under IRB approval procedures when appropriate.		
5	At least one parent or guardian is able to provide informed consent.		

Exclusion Criteria			
	A patient who meets any of the following criteria will be excluded from the study.	Yes	No
1	Patient has alopecia totalis, alopecia universalis, or alopecia areata with ophiasis pattern.		
2	Known allergy or hypersensitivity to triamcinolone acetonide		
3	Pregnant, breastfeeding, or planning to get pregnant 4 weeks before, during, and 4 weeks after the study.		
4	Patient is unable/unwilling to provide informed assent when applicable.		
5	Known medical diagnosis or use of a medication that alters pain response at time of injection.		
6	Active infection at site designated for injection.		
7	If currently being treated for alopecia areata, the current treatment regimen has been started within less than 4 weeks of screening.		

Number of Research Participants

This is a proof-of-concept pilot study. Collins et al. stated that the boundary between mild and moderate pain is a numerical rating scale (NRS) score of 3 (Collins 1997). Previous use of needle-free delivery methods have demonstrated an NRS < 3 (Nantel-Batista 2017, Vadeboncoeur 2017). Based on previous studies and the pilot nature of this study, 15 subjects will be enrolled to determine whether mild or moderate pain would be anticipated in future large scale assessments.

Recruitment Methods

We will be recruiting patients from Northeast Ohio ages 6-17 years with patchy alopecia areata. Subjects will be recruited from the Pediatric Dermatology RBC Zagara Clinic by Dr. Sonal Shah, the Dermatology Clinical Trials Unit Database, and from dermatology provider referrals at University Hospitals practices on main campus, Beachwood, Twinsburg, Independence, Westlake, Cuyahoga Falls, and Concord. Patients identified from the clinical trials database will be approached by a letter of recruitment. We will also perform a Trinetx search of the EMR database to identify potential patients; we will contact the providers for these patients for permission to contact the patients and their parents. If identified by provider referral, the referring provider will inform the patient that a member of our clinical trials research group will contact them. A follow-up phone call will be done under the guidelines outlined in the interview guide. In addition, flyers will be placed in clinical areas and patients and their parents may inquire about joining the study by calling the phone number on the advertisement flyer in our dermatology outpatient clinics. The purpose of the phone interview questions is to pre-screen participants prior to commitment of a screening visit. Clinical trials staff may also pre-screen the EMR during the phone interview to aid with interview guide questions. After the initial prescreening phone call, patients will be asked to come to the clinic to begin the screening visit.

Setting

The research team recruitment efforts and all research procedures will be performed in the dermatology outpatient clinic at UH RBC Zagara Clinic, University Hospitals Cleveland Medical Center, Bolwell 3100 outpatient dermatology clinic, at the Department of Dermatology Skin Study Center, or at University Hospitals Dermatology, 2820 West Market Street, Suite 210, Fairlawn, OH 44333.

Consent Process

Subjects will be consented during the screening visit in a private patient room located at UH RBC Zagara Clinic. University Hospitals Cleveland Medical Center, Bolwell 3100, outpatient dermatology clinic, at the Department of Dermatology Skin Study Center, or at University Hospitals Dermatology, 2820 West Market Street, Suite 210, Fairlawn, OH 44333. Subjects will initially review the consent document with the study coordinator/study physician. After this initial review, the subjects, will be given the opportunity to review independently, discuss the study with family/friends/etc., and then ask the study team their questions or concerns prior to signing the consent. Subjects can take as much time as they need before deciding to participate or not to participate in the study. To ensure participant understanding of the study, the participant will be asked to explain the study back to the coordinator consenting the subject. To minimize coercion, participants will be given time to review the consent alone before deciding. The study coordinator will explain to the participant that their decision to participate/not participate will not impact their standard/routine clinical care.

Study Design

This is an interventional pilot study assessing the tolerability of needle-free delivery administration of ILTA with the Med-Jet as an alternative to conventional syringe and needle in patients with patchy pediatric alopecia areata. There will be a total of four (4) or five (5) visits necessary for study participation. We hypothesize that the Med-Jet will have acceptable pain tolerability, efficacy, safety, and a positive impact on patient quality of life.

Study Procedures

- **Informed Consent**
    - An Informed Consent Form (ICF) will be signed by at least one parent or guardian before any study-related assessments are performed. Assent will be elicited when applicable prior to any study-related assessments being performed.
- **Study Visits**

  There will be four (4) or five (5) visits necessary for study participation:
    - If all inclusion criteria are met and no exclusion criteria are met on the same day and the patient and their guardian wish to start the study, the baseline visit and screening visit can be completed on the same day. This will decrease the number of visits from 5 to 4. o
    - If the patient has complete hair growth prior to the end of the study, they will complete all remaining visits, but they will not receive injections.
    - *Visit 1 Screening (within 5 weeks prior to baseline visit or same day, estimated time 1 hour if baseline activities are not performed):*
        - We will obtain informed consent, review inclusion/exclusion criteria, obtain medical history (medical conditions, surgeries, alopecia areata history, medications, allergies, social history, and relevant family history), obtain vitals, perform a complete skin exam, efficacy assessments, patientreported pain assessments, and quality of life assessments. A urine pregnancy test will be performed for persons of childbearing potential.
    - *Visit 2 Baseline (Week 0, estimated time 1.5 hours if not performed the same day as screening):*
        - This will be the in-office intervention visit to be scheduled within 4-6 weeks of screening visit. We will review inclusion/exclusion criteria, obtain concomitant medications, adverse events (AE), obtain vitals, perform limited skin examination with efficacy assessment, photograph of target lesions, perform intervention injections per protocol, collect patientreported pain assessments and quality of life assessments. A urine pregnancy test will be performed for persons of childbearing potential.
    - *Visits 3-5 Follow up study period (Week 4, 8, and 12, estimated time 30 minutes each):*
        - A limited skin exam, photographs, review of AEs and concomitant medications, efficacy assessments, QoL assessments and pain assessments will be performed. ILTA will be administered at each visit unless complete regrowth has occurred. A urine pregnancy test will be performed for persons of childbearing potential.

Inclusion/Exclusion Criteria

Subjects must meet all inclusion criteria and must not meet any exclusion criteria to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study.

Past Medical History and Surgical History

All medical, surgical, and social history, as defined in the electronic Case Report Form (eCRF) Completion Guidelines and the Study Manual, will be recorded. The date of medical diagnoses and surgical procedures will be recorded.

Prior and Concomitant Medications and Therapies

All medications and therapies being taken/used by the subject at the time of consent or at any time during the study will be recorded. All medications and therapies for alopecia areata, will be recorded. The stop dates and reason for stopping all medications and therapies prohibited in the study will be recorded.

- **Intervention**
    - At least two patches; each measuring 2 cm2 and at least 1 cm from one another will be identified, mapped out, and photographed.
    - Only one of the alopecic patches will be treated.
    - The concentration of ILTA will be controlled at up to 1 mg per cubic centimeter (0.1 ml @ a maximum concentration of 10mg/ml) injected every 1 cm until patch has been fully treated. The researcher providing treatment will be properly trained to deliver intradermal injections using the syringe and needle-free system.
    - **Med-Jet with Triamcinolone (TAC) Procedure** - ILTA will be administered into the patches. The PI and co-investigators will be performing interventions and follow proper training by the manufacturer on operation and handling of the device. Training will consist of a live course with a designated manufacturer technician supplemented with training videos. A standard sterile disposable 5 ml syringe will be used to draw TAC using standard sterile protocol. This syringe will be attached to the Med-Jet along with a sterile barrel and disposable sterile tip. The target lesion will be wiped with alcohol and injected with up to 10mg/ml of TAC directed towards the dermis to create a blanching wheal that is 1 cubic centimeter (total of 0.1 ml of injected fluid). The optimal injection pressure used on the subject will start at 130 pounds per square inch (psi) and increased by 5 psi until a blanching wheal is observed. The optimal pressure will be recorded. The injections will be repeated multiple times at the optimal pressure until the targeted patch is completely treated.
    - Patients will be treated at each visit unless complete regrowth has occurred. Photographs will be taken at each visit and activities will be completed as above.

Safety Assessments

- **Full Skin Exam/Limited Skin Exams/ Photographs** A full skin examination includes evaluation of all cutaneous and mucosal surfaces. A limited skin exam includes only evaluation of the scalp. Photographs of affected skin will be completed each visit. Patient can decline examination of breasts, buttocks, and genitals during the full skin exam.
- **Pregnancy Surveillance & Contraception Education** Subjects of childbearing potential will require a urine pregnancy test at each visit.
- **Monitoring Adverse Events** Details of adverse event reporting may be found in section 6.

Clinical Assessments

- **Physician Efficacy Assessments**
    - **Severity of Alopecia Tool (SALT) Score** The SALT score is a visual tool to help assess percentage of hair loss on the scalp. The scalp is divided into four sections – top, back, right side, and left side. Each section contributes to a total of 100% (i.e. top = 40%, back = 24%, sides = 18% each). Raters assess total percentage of hair loss in the section and then multiple is by the respective multiplier which is based on that sections total percentage of the scalp – 40%, 24%, or 18%. Only terminal hairs are considered hair growth in this tool. (Olsen et al. 2004) Figure 1 illustrates the visual aid and allows for intuitive use. This is a static tool and only quantifies the hair loss at one point in time.
    - **Alopecia Areata - Investigator Global Assessment (AA-IGA)** The AA-IGA categorizes the scalp hair loss into 5 categories based on the SALT score. The five categories are: 1 = None, 2 = Limited, 3 = Moderate, 4 = Severe, and 5 =Very Severe. The corresponding SALT scores for each category are: 1 = 0%, 2 = 1-20%, 3 = 21-49%, 4 = 50- 94%, and 5 = > 95%. This is a static tool and only quantifies the hair loss at one point in time (Olsen 2004).
    - **"Rule of Thumb" Assessment and Regrowth Categorization** A patient's thumbprint projection is approximately 1% of the scalp surface area (King 2019). When selecting the alopecic patch for treatment and its comparator, thumb projections will be used to quantify the percentage of total scalp hair loss contributed by each these patches at baseline. At each subsequent visit, the thumbprint projection from baseline will be used to determine percent of regrowth since baseline. Based on regrowth, the patient will be categorized into one of 6 categories: A0-5. Where A0 = no change or further loss, A1 = 1-24% regrowth, A2 = 25-49% regrowth, A3 = 50-74% regrowth, A4 = 75-99% regrowth, and A5 = 100% regrowth.
- **Patient-Reported Efficacy Assessments**
    - **Patient-Reported Hair Loss – Whole Scalp** This assessment will apply to the subject's whole scalp surface area. This question will be asked at every visit. And it will include 5 numerical categories: 0 = No missing hair (0% of my scalp is missing hair; I have a full head of hair); 1 = limited area (1% to 20% of my scalp is missing hair); 2 = moderate area (21% to 49% of my scalp is missing hair); 3 = large area (50% to 94% of my scalp is missing hair); and 4 = Nearly all or all (95% to 100% of my scalp is missing hair).
    - **5-Point Patient-Reported Regrowth – Whole Scalp and Selected Patches** At each visit after the baseline visit, the subject will be asked about their perceived amount of hair regrowth both for the whole scalp and those patches selected at baseline. The subject will be able to select one of 5 categories: 1 = Further Loss, 2 = No Change, 3 = A Little Improved (<50% regrowth), 4= A lot of improvement (50-99% regrowth), and 5= Complete Regrowth (100%).
- **Pain Score Assessment**
    - Subjects will rate their pain using the Wong-baker FACES scale (Garra 2010) and a numerical rating scale (NRS) before and after the procedure. The NRS score ranges from 0-10 where 0 is no pain and 10 is the worst pain imaginable (Williamson 2005).

- **Quality of Life Assessment**
    - Subjects 6-11 years of age will use the Children's Dermatology Quality of Life Index (cCDLQI) at each visit (Lewis-Jones 1995). Subjects 12-17 years of age will use the Teenager's Quality of Life Index (T-QoL) at each visit (Basra 2018). Assessments should be performed prior to ILTA administration when applicable.
- **Patient Survey**
    - Participants will be given a survey at each visit. This will assess perceived tolerability, comfortability, associated fear, and assess experience and preference over conventional needle and syringe.

Study Timeline

The following chart lists the standard of care for treatment of patchy pediatric alopecia with ILTA. Each visit can be completed within + 7 days of the target date. Screening and baseline visits can be completed on the same day if appropriate.

	Screening	Baseline	Study Period		
Visit	V1	V2	V3	V4	V5
Week	-4-0	0	4	8	12
Estimated time requirement of visit	1 hour	1.5 hour	30 min	30 min	30 min
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Demographic Data	X				
Past medical and surgical history	X				
Alopecia Areata History	X				
Medications	X				
Allergies	X				
Vital signs (plus height and weight)	X	X			
Full Skin Examination	X				
Limited Skin Examination		X	X	X	X
Laboratory assessments					
Urine pregnancy test*	X	X	X	X	X
Intralesional triamcinolone acetonide		X	X	X	X
Photographs		X	X	X	X
Adverse events		X	X	X	X
Concomitant medications		X	X	X	X
Efficacy Assessment	X	X	X	X	X
Pain Assessment		X	X	X	X
Quality of Life Assessments		X	X	X	X
Patient Survey		X	X	X	X

*Required for all persons of childbearing potential at each visit.

Data to be Collected

- Personal information (name, address, contact information, social security number)
- Medical records
- Personal medical history including medications and allergies
- Vital signs and physical exam findings
- Photographs
- Pregnancy laboratory test results if person of child-bearing potential
- Safety Data (Reported AEs)
- Efficacy Data (tPGA, pruritus score)
- Tolerability Data (Pain Score)
- Quality of life Data (DLQI, Patient survey)

Data Analysis Plan

Statistical analyses will be completed under the supervision of a statistician. Statistical analysis will be done by statistical software (e.g. SPSS, SAS, R, Excel; etc.) AUROC will be calculated in order to assess for accuracy. The $\chi 2$ test may be used for comparison of dichotomous variables, and the Mann-Whitney test may be used for non-normally distributed continuous variables. The cutoff value for significance was set at $p = 0.05$.

Risks to Research Participants

- **Intralesional Injections**
    - Injections with the Med-Jet – Discomfort, bruising, injection site reaction (redness, swelling, pain), and infection
- **Skin evaluations**
    - Minimal emotional discomfort and embarrassment can be considered a risk
- **Questionnaires**
    - Minimal emotional discomfort can be considered a risk
- **Breach of Confidentiality**
    - Study participant information collected in the research process may include; contact information, consent documentation, demographics, social security number (necessary for reimbursement), and personal medical history. All data will be stored on the secure UH or REDCap© server, or as paper records stored in a locked cabinet. Data collected in this study will include: Patient records collected electronically and on paper, consent forms, and urine samples. While we maximize our ability to secure private information, participants could potentially be at risk for anticipated problems such as:
        - Lost or stolen laptops/cabinets storing participant information
        - Faxes sent to the wrong fax machine outside of the Health Sciences Center
        - Paper without PHI not disposed of properly - i.e. shredded
        - Information delivered to the wrong participant using the postal service, courier, or other delivery method

Provisions to Protect the Privacy Interests of Research Participants

The formal consent process and study visits will take place in a private exam room at our outpatient dermatology clinic. Each participant will have the study explained in its entirety with special attention to the length of the study, the actual study procedures, financial obligations, risks, benefits and alternatives to participation. Participants will be given ample time to consider study participation and encouraged to discuss with significant others, have any questions answered by the study staff. Only participants willing to undergo all study procedures will be asked to affirm participation by signing the consent form. Only study staff that have been trained on the study and having IRB required Human Subject Protection Training and authorized by the investigator will obtain consent. Subjects will be reminded the importance of adhering to all study requirements and their right to withdrawal at any time without affecting the quality of their individual medical care. Each class of data will be handled in the following manner:

- Patient Records, Consent Forms, and Study Data:
    - Patients enrolled into the study will complete informed consent and provide medical history. All patients upon entering the study will be assigned a unique identifier by REDCap© that will be used throughout the study to de-identify their information. Consent forms and paper records will be filed in study binders, stored in a locked room within the Department of Dermatology. Only authorized research personnel will have access to these records.
    - Patient records will be created and stored electronically on both the secure and encrypted University Hospitals server and the secure REDCap© server. REDCap© has been adopted and adapted specifically for our use on the CTSC under licensing terms with Vanderbilt University and has been approved for Vanderbilt, in collaboration with a consortium of leading research institutional partners who were funded by both Vanderbilt and the NCRR, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap© data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the CTSC Informatics Core resources. The iterative development and testing process results in a well-planned data collection strategy for individual studies. Whether a study is submitted for scientific review on one of the three CTSC Clinical Research Units, each with a full-time dedicated informatics resource available to support investigators with REDCap©, or an institutional request outside of the controlled environment of the CWRU, our CTSC has made the REDCap© tool and associated resources available for use.
    - The REDCap© survey, a powerful tool for building and managing online surveys as the research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. Both REDCap and REDCap Survey systems provide secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails and reporting for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R), and are managed in-

house by dedicated resources, including for backup/recovery to prevent data loss due to equipment failure.
    - The PI will ensure protocol adherence, proper protocol conduct, data quality, and subject safety and efficacy by conducting regular meetings with the entire study staff. The adverse events submitted by subject phone inquiry or email will be reviewed and adjudicated with all research team members. In addition, any adverse events or deviations to the protocol or other issues will be discussed at the Regulatory Meeting held monthly in the department of Dermatology.
- **Tissue Samples:** No tissue samples will be taken in this study.
- **Photographs:** All photographs will be de-identified and stored on the secure UH server, only accessible to authorized study personnel. In the event a photograph is taken of the face or any other identifiable feature, the patient's identity may become known.
- **Data Transfer/Transmission:** Research data will be sent to a statistician for data management after finishing this research study: however, all the data will be stripped of patient identifiers prior to transfer. In order to comply with federal regulations, records identifying participants in this study may be reviewed by authorized study personnel, authorized representatives of the Institutional Review Board, or other federal regulatory officials responsible for oversight of human subject protection. Any data linking participants to their sample will be deidentified. A code will be used to link participants to identifying information and only the investigators and the research study coordinators will have access to this information, which will be stored on a server at University Hospitals Case Medical Center with a separate encryption code. Upon enrollment, each patient record will be stripped of all identifying information and assigned a unique numerical identifier that has no reference to any identifiable patient information.

Potential Benefit to Research Participants

In this study no benefits to the study subjects for participating in this research can be guaranteed, though some patients may experience improvement of their treated alopecic patches. Information gained from this study may improve therapies for patchy pediatric alopecia areata by demonstrating that needle-free drug delivery systems can be used safely and effectively.

Withdrawal of Research Participants

The participants are entitled to withdraw from the study at any time and for whatever reason without this influencing their access to the treatment via the investigator. We do not anticipate any circumstances that will require participants to be withdrawn from the research by the study investigator without their consent.

Alternatives to Participation

The only alternative for potential subjects is to not participate.

Costs to Research Participants

Study drug and all study procedures required by the study will be funded by the department of dermatology under the supervision of the principal investigator. Costs for medical treatment as a result of research-related injury will not be funded. Parking for all study-related visits will be validated.

Research Participant Compensation

The participant will be compensated a parking voucher for completion of each study visit.

Provisions to Monitor the Data to Ensure the Safety of Research Participants

Procedures for analysis and interpretation of data: The PI has meetings with the staff performing both the clinical and laboratory based assessments. These meetings occur on a minimum of a monthly basis, but often occur more frequently. These meetings are held for two primary functions: The meetings are, first, to discuss primary data and progress of the study. Data include both clinical observation and laboratory measurements. The secondary function of these meetings is to monitor clinical outcomes for potential adverse events associated with the study. The PI has put into place an action plan should adverse events occur during the course of the study. Adverse events that could be envisioned are outlined below:

A. **Responsible party for safety monitoring:** In addition to the PI, safety monitoring will also be performed by the University Hospitals Data Safety and Monitoring Committee.
B. **Safety Monitoring Methods and Intervals:** Grading method and attribution for adverse event reporting AE will be graded according to the following 0-5 scale:

Score	Description
0	No Adverse Event or within normal limits or not clinically significant
1	Mild AE did not require treatment
2	Moderate AE resolved with treatment
3	Severe AE resulted in inability to carry on normal activities and required medical attention
4	Life threatening or disabling AE
5	Fatal AE

The PI will determine the relationship of AE's to the test procedure/agent/device as; not related, possibly related, or definitely related, using standard criteria for clinical trials.

- All reported AEs will be followed until the event resolves or stabilizes OR
- The event returns to baseline OR
- The event can be attributed to agents other than the study agent(s) OR
- The subject withdraws informed consent OR
- The subject is lost to follow up.

Implementation of the data and safety monitoring plan: The study team will internally review AEs at each patient visit and weekly with the PI. The study team will notify the DSMC of any Grade 3+ events within 1 week, and that the DSMC will formally review the study every 6 months. Adverse event reports for this protocol will be submitted to the approved IRB. Adverse Event Report Form sent in a timely manner consistent with the approved IRB policy.

In addition, any serious adverse event (grade 3 or greater), except for those reported in the protocol, must be reported to the sponsor by the investigator by telephone, fax or email within 24 hours. A

notification form will then be sent to the sponsor by fax or email with acknowledgement of receipt within 48 hours of the event.

The investigator will also inform the sponsor of adverse events and abnormal results of the analysis, which are defined as decisive for the evaluation of safety of persons taking part in biomedical research.

Drugs or Devices

- Triamcinolone acetonide injection therapy
    - Triamcinolone acetonide is not being trialed in this study. It is only included here for informational purposes given its significant role in our study.
    - **Mechanism of Action:** Triamcinolone is an organic lipophilic compound under the class of glucocorticoids which has a vast role in treatment of inflammatory skin conditions. It is proposed that TAC binds to glucocorticoid receptors in the cytoplasm and undergoes conformational changes. This drug-protein complex directly binds to DNA affecting gene regulation and transcription of various specific messenger ribonucleic acid (mRNA). In the skin, this leads to reduction of proinflammatory cytokines, t-cell lymphocytes, and suppression of keratinocyte growth factors. This is particularly helpful in psoriasis as cytokine/t-cell dysregulation and keratinocyte hyperproliferation is the pathogenic hallmark. In the dermis, glucocorticoids suppress fibroblasts activity and collagen/elastic fiber production which can lead to dermal volume reduction and subsequent dermal atrophy seen clinically.13
    - **Dosing, Formulation, Frequency:** Multiple formulations of triamcinolone acetonide exist including lotions, topical spray, nasal spray, cream, ointment, dental paste, and injectable suspension. The injectable suspensions are produced in two concentrations, 10mg/ml or 40mg/ml. In our study we will be performing injections using the 10mg/ml injectable suspension to inject up to 1 mg of TAC per cubic centimeter to minimize drug-related adverse events. The TAC may be diluted with sterile saline to a concentration less than 10 mg/ml. After one intervention of TAC, the first signs of involution start 4-14 days after injection with max involution at 2-3 months, followed by relapse at 6-12 months at which a repeat intervention may be considered.14
- Med-Jet Injector
    - The Med-Jet injector is a needle-free injection system which consists of a handheld firing body/trigger, sterilized barrel, disposable luer lock syringe, disposable nozzle cap, and disposable splash guard. The Med-Jet injector is designed to deliver drugs or biologics into the intradermal, subcutaneous or intramuscular tissues, by means of a narrow, high-velocity jet of fluid, which penetrates the surface of the skin and delivers the fluid to the target tissue. Upon attenuation of the trigger, the device uses regulated compressed carbon dioxide (CO2) or compressed air as a power source to accelerate an injectable fluid through a small orifice (0.005”) in a fraction of a second. The dose volume can be pre-set with an adjustment knob at an accuracy of ±0.0125ml for 0.25ml injections. The depth of injection is also adjustable based on pressure as denoted by pounds per square inch (psi) which in our study will be targeting the dermis at an average 140 psi which is needed to create a wheal (Nantel-Battista 2013). Upon release, the dose chamber is automatically refilled and ready for the next actuation for multiple injections.

- The needle-free drug delivery system with triamcinolone could be more efficacious then using a conventional syringe due to the dispersion physics of forcefully propelling a fluid into the skin [Schramm-Baxter 2004; Park 2015). Jet propulsion results in a sporadic-shaped distribution of fluid under the skin when compared to a bolus-shape using conventional syringes. The dispersion of fluid made by jet propulsion could be valuable delivering triamcinolone to the dermis in patchy pediatric alopecia areata (Meah et al 2020).
- Administering ILTA using the needle-free drug delivery system will have a similar safety profile to conventional syringes with some additional benefits. One benefit of a needle-free system is the zero-risk of needle-stick injuries on providers. Lipoatrophy, a rare side effect of ILTA when injected too deep and in proximity to the subcutaneous fat, could be minimal with needle-free injections due to the operator-controlled injection depth parameter. Reported complications of needle-free injections were seen with devices using high driving pressures (1,420 psi); however, in this study, we will be using a low-pressure system (< 160 psi) (Seok 2016; Barolet 2018; Haneke 2012) This method of ILTA delivery has been used in the hyperhidrosis or nail psoriasis trials and none of the subjects encountered significant adverse effects with a low-pressure system (Vadeboncoeur 2017, Nantel-Battista 2014). This device is not currently approved for use in the United states by the FDA. We are requesting a determination from the IRB for investigational use of the Medjet as a nonsignificant risk medical device.
- The Medjet needle-less system propels an injectable fluid through a 0.005” orifice which is 6x smaller than a 30G needle (MedJet)> The small orifice combined with a quick delivery low-pressure system results in decreased pain scores for patients. In the nail psoriasis trial, 17 patients were injected over the proximal nail fold, which is a rather sensitive area, and reported a mean pain score of 2.1 based on a 10-point scale (Nantel-Battista 2017). Similar results were seen in the hyperhidrosis trial with scoring an average 3 on a 10-point scale over the palms (Vadeboncoeur 2017). Finally, the absence of a needle will create a more tolerable environment for patients who are needle phobic.

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