Iontophoresis with Dexamethasone in Combination With Physical Therapy for the Treatment of Pediatric Patients Diagnosed with Apophysitis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Trial

IND # - 140701

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
4.1	Removed reference to no planned interim analysis.	
9.4.7	Added Interim Analyses	

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STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, United States Code of Federal Regulations (CFR) 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and applicable state, local, and federal regulatory requirements.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will be reviewed and approved by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination by the IRB will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

All personnel involved in the conduct of this study have completed Collaborative Institutional Training Initiative (CITI) Training in Human Subjects Research.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Iontophoresis with Dexamethasone in Combination With Physical Therapy (PT) for the Treatment of Pediatric Patients Diagnosed with Apophysitis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Trial

Study Description: This trial is a three-arm, randomized, double-blind, placebo-controlled comparison study looking at the functional and patient reported outcomes of iontophoresis (with dexamethasone sodium phosphate (DSP)) or 0.9% sodium chloride (placebo) in conjunction with PT versus PT alone to treat pediatric patients diagnosed with apophysitis of the knee.

The null and alternative hypotheses for the primary endpoint are:
Null Hypothesis: Time to achieve Return To Sport (RTS) criteria for Pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT is the same as those who receive iontophoresis with placebo and PT or PT alone.

Alternative Hypothesis: Time to achieve RTS criteria for Pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT will be different from those who receive iontophoresis with placebo and PT or PT alone.

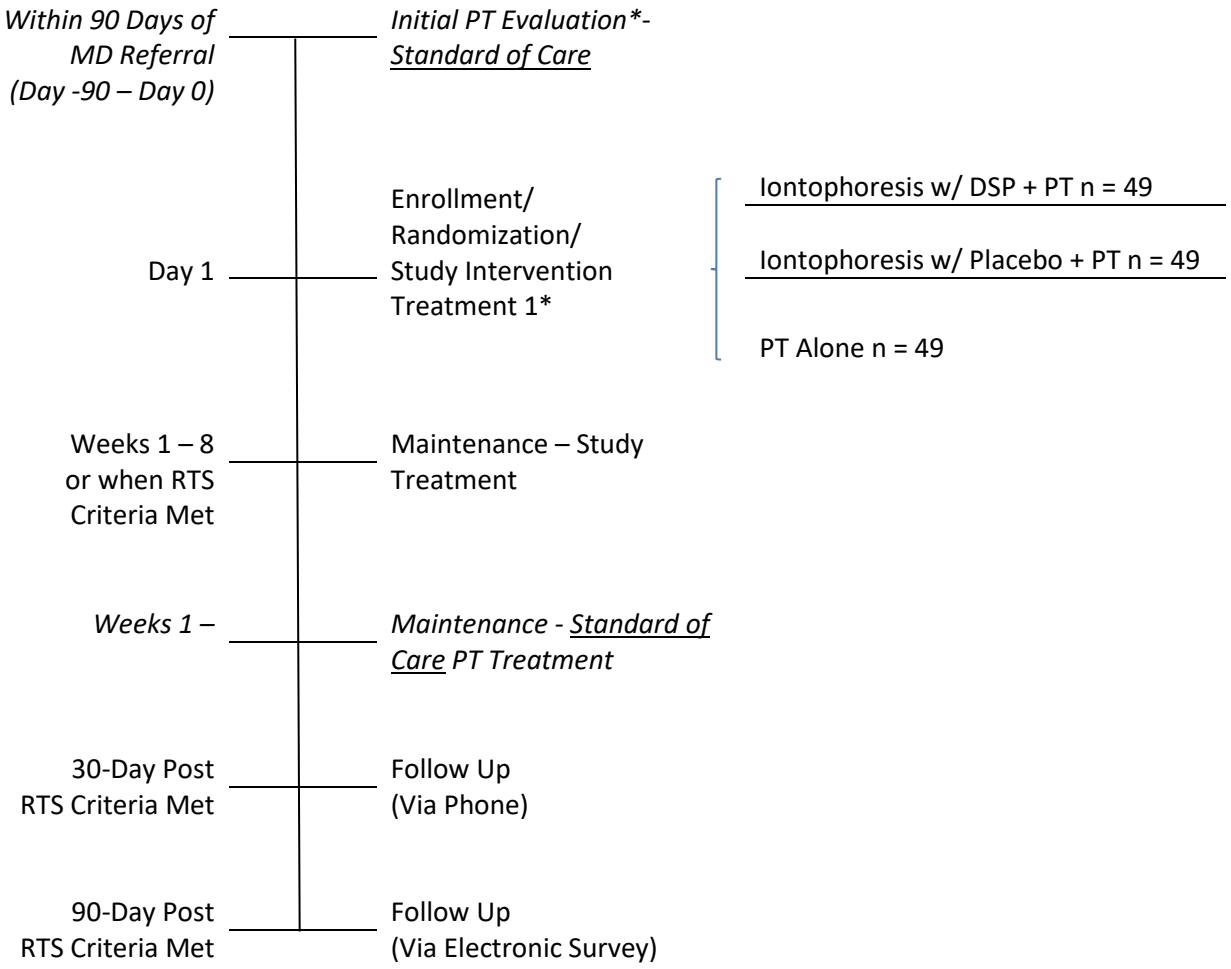
The null and alternative hypotheses for the secondary endpoints are:
Secondary Endpoint (Efficacy) - Patient reported outcomes:
Null Hypothesis: There is not any significant difference in patient reported outcomes (Lower Extremity Function Scale (LEFS), Godin Leisure-Time Exercise, and FACES pain scale) between pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT and

	those who receive iontophoresis with placebo and PT or PT alone. Alternative Hypothesis: Patient reported outcomes (LEFS, Godin Leisure-Time Exercise, and FACES pain scale) of pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT will be different from those who receive iontophoresis with placebo and PT or PT alone. Secondary Endpoint (Safety) : Frequency and intensity of adverse events Null Hypothesis: There is not any significant difference in frequency and intensity of adverse events between pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT and those who receive iontophoresis with placebo and PT or PT alone. Alternative Hypothesis: Frequency and intensity of adverse events among pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT will be different from those who receive iontophoresis with placebo or PT alone.
Objectives:	Primary Objective: - To compare the functional outcomes of iontophoresis with DSP in combination with PT versus iontophoresis with placebo in combination with PT versus PT alone in pediatric patients diagnosed with apophysitis of the knee. Secondary Objectives: - To compare the patient reported outcomes of iontophoresis with DSP in combination with PT versus iontophoresis with placebo in combination with PT versus PT alone in pediatric patients diagnosed with apophysitis of the knee. - To compare the safety of iontophoresis with DSP in combination with PT versus iontophoresis with placebo in combination with PT versus PT treatment alone in pediatric patients diagnosed with apophysitis of the knee.
Endpoints:	Primary Endpoint: - Length of time to meet RTS criteria as measured in days Secondary Endpoints: - Percent difficulty with activities as measured by the LEFS - Patient reported activity as measured by the Godin Leisure-Time Activity Questionnaire - Patient reported pain as measured by the FACES Pain Scale - Safety as measured by number and intensity of iontophoresis or DSP-related adverse events
Study Population:	147 pediatric patients referred by the Children's Hospital of the King's Daughters (CHKD) Primary Care Sports Medicine Physicians and Orthopedic Physicians to the CHKD Sports Medicine PT Department, with a diagnosis of apophysitis of the knee.
Phase:	II
Description of	Participants will be screened, enrolled, and treated at six (6) CHKD Sports

Sites/Facilities Enrolling Participants:	Medicine PT Clinics across the Hampton Roads area.
Description of Study Intervention:	The study intervention is iontophoresis therapy using 4mg/ml DSP in conjunction with standard PT. This will be compared to iontophoresis therapy using placebo with standard PT and standard PT alone. Iontophoresis is a non-invasive delivery mechanism for transmitting a medication to a local area of the body. DSP is a synthetic adrenocortical steroid approved for the use in endocrine, rheumatic, collagen, dermatologic, allergic, ophthalmic, gastrointestinal, respiratory, hematologic, neoplastic, and edematous disorders. DSP is approved by the Food and Drug Administration (FDA) for intravenous, intramuscular, intra-articular, or intralesional administration but not via iontophoresis.
Study Duration:	Study enrollment is estimated to last 40 months, followed by six (6) months of data analysis, for total study duration of 46 months.
Participant Duration:	Each participant's study duration will be approximately five (5) months.

1.2 SCHEMA

Timeline



*-Initial PT Evaluation and Enrollment/ Randomization/ Study Intervention Treatment 1 Visits may be combined and completed on the same day.

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Clinic Visits								**Follow-Up**	
		Study Treatment Visits					Clinic Check	Early Stop Visit		
Procedures (Time to Complete)	Initial Evaluation*	# 1*	# 2 - # 4	# 5	# 6 – # 11	# 12 or Week 8, or when Return To Sport Criteria Met			30 –Day By Phone	90-Day By Survey
Standard PT Treatment	X									
Standard PT Treatment		X ----------X								
Inclusion/ Exclusion Criteria		X								
Informed Consent		X								
Randomization		X								
FACES Pain Scale		X	X	X	X	X	X	X		
Brief Physical Exam of the Targeted Knee		X	X	X	X	X	X	X		
Medication Review		X	X	X	X	X	X	X	X	X
Adverse Events Evaluation		X	X	X	X	X	X	X	X	X
Lower Extremity Functional Scale (LEFS)		X		X		X		X	X	
Return to Sport Criteria (RTS) Checklist		X	X	X	X	X	X			
Godin Leisure-Time Exercise Questionnaire		X							X	X
Compliance Check to Home Exercise Program, Patch Wear Time, Ice Application, Bracing, and Activity Restrictions		X	X	X	X	X	X	X		
Iontophoresis Treatment (Groups A and B only)		X----------X								
Complete Case Report Forms		X	X	X	X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Apophysitis refers to pain and inflammation at the apophysis, or secondary ossification center, thought to occur secondary to repetitive tensile stress at the tendinous attachment to the bone.[1] Apophysitis of the tibial tubercle was first described in 1903 separately by Osgood and Schlatter.[2] Osgood Schlatter Disease (OSD)was described as the painful separation of the epiphysis of the tibial tuberosity occurring in children and adolescents undergoing rapid growth, placing stress on the developing tibial tubercle through patellar tendon force.[3] It is theorized that traction apophysitis and traumatic avulsion of the secondary ossification center occurs during the apophyseal stage of maturation of the tibial apophysis.[2] Males commonly become symptomatic between the ages of 12 and 15 years old and females develop pain between the ages of 8 and 12 years old.[2] OSD affects 21% of athletic adolescents and 4.5% of aged matched nonathletic controls.[4] Sinding-Larsen-Johansson (SLJ) Syndrome is similar to OSD in that it is due to traction apophysitis from the extensor mechanism except in SLJ the traction occurs at the inferior pole of the patella at the patellar tendon insertion. It occurs most commonly in boys age 11-13 years old.

Individual's history and physical exam are typically sufficient to make a diagnosis. Patients usually present with a vague history of a gradual onset of pain and mild swelling overlying the tibial tuberosity. In both cases, pain is exacerbated after activities involving running and jumping as well as those with direct contact over the tibial tuberosity or patella such as kneeling.[3]

In OSD, plain radiographs often show irregularity of the apophysis with separation from the tibial tuberosity in early stages and fragmentation of the apophysis in later stages. In SLJ, radiographs may show irregular ossification or fragmentation of the inferior pole of the patella which ultimately will fuse to the patella during growth.

There are no prospective randomized controlled interventional studies evaluating the treatment of OSD or SLJ. Both are self-limited diseases and generally cease with skeletal maturity.[3] All data and evidence regarding treatment are from retrospective studies. Initial management is non-operative and consists of rest, ice, oral anti-inflammatory medications, protective knee padding and PT.[1] Patients with mild pain often continue their normal sports and activities while those with more severe pain benefit from rest or change to low impact sports and activities. OSD and SLJ often result in pain with activities of daily living, decreased participation in sports and physical education, and decrease activity, fitness and socialization.

2.2 BACKGROUND

The purpose of this double-blind placebo-controlled study is to evaluate the effects of treatment with DSP iontophoresis as an adjunct therapy with PT in pediatric patients with apophysitis of the knee. Patients diagnosed with OSD or SLJ will be randomized to one of three treatment groups: treatment DSP iontophoresis and PT, iontophoresis with placebo and PT, or PT alone. This study will compare the functional and patient reported outcomes of each group.

Iontophoresis has been used clinically for over 50 years to deliver drugs transdermally to localized areas of inflammation. Iontophoresis uses a mild electrical current to "push" ionic compounds through the skin and usually increases the rate and extent of absorption compared with passive treatments like the applications of creams, gels or ointments.[5] The most common drug used clinically for musculoskeletal pain delivered by iontophoresis is DSP. DSP is a phosphate ester prodrug of DSP that transforms the highly lipophilic DSP into a water-soluable molecule suitable for injection. The water solubility and two ionizable groups of DSP make it an ideal candidate for transdermal iontophoresis. Iontophoresis delivers significantly more DSP solution across in vivo human skin compared to passive delivery.[5]

While iontophoresis of DSP is widespread and has been used for decades in musculoskeletal conditions, studies evaluating its benefits in musculoskeletal conditions have been mixed. Some studies have shown improved outcomes in pain and function in a number of musculoskeletal conditions, whereas other studies have shown no benefits.[5] There have been no studies evaluating its use in the treatment of OSD or SLJ.

Epicondylitis or "tennis elbow" is the musculoskeletal condition DSP iontophoresis has been evaluated with most. One high quality randomized control trial of DSP iontophoresis for epicondylitis showed significant short-term improvement in pain and global function compared to placebo when treatment concluded, although benefit did not persist at one month follow up.[6] Another high quality randomized control trial of DSP iontophoresis use in epicondylitis showed no short or long term improvement in pain or strength compared to placebo.[7] A high quality randomized controlled trial in mild to moderate carpal tunnel syndrome comparing DSP iontophoresis to iontophoresis with distilled water showed no significant improvement in patient reported outcome scores or on nerve conduction studies.[8] When used as a treatment for acute Achilles tendonitis in a double-blind study, DSP iontophoresis showed positive effects compared to iontophoresis with saline, but the study was underpowered and inconclusive.[9]

While DSP iontophoresis has been used to treat musculoskeletal conditions for decades, there are few high quality studies evaluating its use in this manner. Data supporting its use has been at best mixed. No studies on DSP iontophoresis use in OSD or SLJ exist, but it is commonly used for these indications. Our study will be the first to evaluate DSP iontophoresis for these conditions. The limited studies done on the use of DSP iontophoresis for musculoskeletal conditions demonstrates the importance of performing a high quality trial.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 Iontophoresis

- May cause mild tingling, prickling and/or warm sensation – this is normal and should be anticipated by the participant
- Redness underneath the application site used for iontophoresis
- Dryness or rough skin in area where the iontophoresis was administered
- Skin discoloration or hyperpigmentation

- On rare occasions, iontophoresis therapy can result in transient skin reactions such as rash, inflammation, irritation or burns (blistering). These skin reactions may be the result of:
    - individual sensitivity to the ionic solution used
    - the condition of the skin at the onset of treatment
    - reaction to the materials in the electrodes
    - a poor connection between the electrode and the patient's skin.

Participants will be instructed that if the treatment becomes painful, or if they experience a burning sensation, or an excessive sensation, they should remove the Patch and notify their Treating Therapist.

2.3.1.2 DSP

DSP is an adrenocortical steroid anti-inflammatory drug commonly used with iontophoresis in physical therapy.[10] DSP, used in this research study, is approved by the FDA for intravenous, intramuscular, intra-articular, or intralesional use.[11] The contraindications, warnings, and precautions associated with intravenous, intramuscular, intra-articular, or intralesional use are well outlined in the drug package insert. However, for this study, and in line with standard practice, DSP will be administered via iontophoresis, a route of administration not approved by the FDA.

Literature shows delivering medication via iontophoresis requires a smaller dose of medication than by other routes of administration, is non-invasive, and delivers the medication locally versus systemically, minimizing the risks of adverse drug reactions.[10] There is no published data on the systemic effects of DSP administered via iontophoresis.

Although not expecting systemic side effects, in the absence of published data, below are listed possible side effects, warnings, and precautions when DSP is given for intravenous, intramuscular, intra-articular, or intralesional use.

When given for intravenous, intramuscular, intra-articular, or intralesional use:

Known systemic side effects:
 	
• *Fluid and electrolyte disturbances:*
  ○ *Sodium retention*
  ○ *Fluid retention*
  ○ *Congestive heart failure in susceptible patients*
  ○ *Potassium loss*
  ○ *Hypokalemic alkalosis*
• *Musculoskeletal*
  ○ *Muscle weakness*
  ○ *Steroid myopathy*
  ○ *Loss of muscle mass*
  ○ *Osteoporosis*
  ○ *Vertebral compression fractures*
  ○ *Aseptic necrosis of femoral and humeral heads*

When given for intravenous, intramuscular, intra-articular, or intralesional use:

- *Pathologic fracture of long bones*
- *Tendon rupture*

- *Gastrointestinal*
  - *Peptic ulcer with possible subsequent perforation and hemorrhage*
  - *Perforation of the small and large bowel, particularly in patients with inflammatory bowel disease*
  - *Pancreatitis*
  - *Abdominal distention*
  - *Ulcerative esophagitis*
- *Dermatologic*
  - *Impaired wound healing*
  - *Thin fragile skin*
  - *Petechiae and ecchymoses*
  - *Erythema*
  - *Acne*
  - *Increased sweating*
  - *May suppress reactions to skin tests*
  - *Burning or tingling, especially in the perineal area (after I.V. injection)*
  - *Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema*
- *Neurologic*
  - *Convulsions*
  - *Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment*
  - *Vertigo*
  - *Headache*
  - *Psychic disturbances*
- *Endocrine*
  - *Menstrual irregularities*
  - *Development of cushingoid state*
  - *Suppression of growth in children*
  - *Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness*
  - *Decreased carbohydrate tolerance*
  - *Manifestations of latent diabetes mellitus*
  - *Increased requirements for insulin or oral hypoglycemic agents in diabetics*
  - *Hirsutism*
- *Ophthalmic*
  - *Posterior subcapsular cataracts*
  - *Increased intraocular pressure*
  - *Glaucoma*
  - *Exophthalmos*
- *Metabolic*
  - *Negative nitrogen balance due to protein catabolism*
- *Cardiovascular*
  - *Myocardial rupture following recent myocardial infarction*

When given for intravenous, intramuscular, intra-articular, or intralesional use:

- *Hypertension*
- *Cardiac dysrhythmia*

- *Other*
  - *Anaphylactoid or hypersensitivity reactions*
  - *Thromboembolism*
  - *Weight gain*
  - *Increased appetite*
  - *Nausea*
  - *Malaise*
  - *Hiccups*
  - *Immunosuppression*

The following warnings/precautions listed in the drug package insert will not be included in the consent form as they are associated with long-term use and the design of this study is for short-term use of DSP:

Warnings/Precautions associated with DSP (when given for intravenous, intramuscular, intra-articular, or intralesional use):

Related to adverse effects:

- *Adrenal suppression – may cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis), particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis*
- *Immunosuppression – prolonged use of corticosteroids may increase the incidence of secondary infection, cause activation of latent infections, mask acute infection, prolong or exacerbate viral infections, or limit response to killed or inactivated vaccines*
- *Kaposi sarcoma – prolonged treatment with corticosteroids has been associated with the development of Kaposi sarcoma in case reports; if noted, discontinuation of therapy should be considered*

Disease-related concerns:

- *Cardiovascular disease – use caution in patients with heart failure, acute MI and/or hypertension*
- *Diabetes – use caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia*
- *Gastrointestinal disease – use caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess or other pyogenic infection) due to perforation risk*
- *Hepatic impairment – use caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention*
- *Myasthenia gravis – use caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids*
- *Ocular disease – use caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. Not*

When given for intravenous, intramuscular, intra-articular, or intralesional use:

recommended for the treatment of optic neuritis; may increase frequency of new episodes

- *Osteoporosis – use caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures*
- *Renal impairment – use caution in patients with renal impairment; fluid retention may occur*
- *Seizure disorders – use caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis*
- *Thyroid disease - Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid one*

Other:
Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients

Participants will be instructed to call 9-1-1 or seek medical treatment at their nearest emergency department if they experience a severe reaction.

2.3.2 KNOWN POTENTIAL BENEFITS

The iontophoresis system allows for the delivery of dexamethasone at a controlled rate to ensure therapeutic efficacy. Due to its continuous medication delivery at a pre-programmed rate, the risk of over or under dosing with iontophoresis is effectively eliminated. As a transdermal drug delivery system, benefits include the avoidance of "first-pass" metabolism, drug-food interactions, gastrointestinal absorption, and enzymatic activity, all of which may be a factor in oral drug administration. In contrast to injections, iontophoresis is a noninvasive method for delivering medication. While it does utilize a direct electrical current, it is typically well-tolerated with minimal discomfort.[12] Iontophoresis using the I-Bresis™ system is a convenient method of dexamethasone delivery, with easy application, performed in clinic by trained therapists.

While there is no specific research regarding the use of iontophoresis with DSP for knee apophysitis, there is literature indicating that it is useful for treatment of pain, resulting in reduction of disability associated with other musculoskeletal disorders.[6,9,13,14,15,16,17] Current literature on Osgood-Schlatter disease describes common use of nonsteroidal anti-inflammatory drugs for a short period of time for decreased prostaglandin synthesis, pain-relief, and anti-inflammatory effects.[3,18] Iontophoresis allows administration of DSP, an anti-inflammatory corticosteroid, without the risks involved with oral ingestion.

While knee apophysitis is described in the literature as a self-limiting condition, it typically results in immediate functional limitations. Individuals with knee apophysitis are often prescribed rest or activity limitations as part of the current recommendations for conservative treatment. This results in limited participation in sports, physical education class, and recreational activities, thereby reducing physical activity, fitness, and socialization with peers. If iontophoresis with DSP is shown to facilitate expedited

recovery of knee apophysitis, it would result in both physical and psychosocial benefits for affected individuals.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The systemic administration of steroids such as dexamethasone is associated with side effects that can affect multiple organ systems in the body including the muscular system, skeletal system, immune system, renal system, digestive system, integumentary system, nervous system, endocrine system, and circulatory system. Since dexamethasone will be administered transdermally in this study and for a short duration of time, we do not expect to see the systemic side effects of the medication. We have minimized the risk to the participants by administering DSP transdermally. The side effects of most concern would be local cutaneous reactions or hypersensitivity reactions.

The benefits of facilitating a quicker recovery from knee apophysitis to allow both the physical and psychosocial benefits previously described far outweigh any small mostly theoretical risk. Any local reaction that could occur is self-limited in time and morbidity. In our almost 20 years in clinical experience of using iontophoresis with DSP we have never seen any significant adverse reaction. However, we have seen thousands of patients improve quickly with the addition of iontophoresis with DSP. From 2009 (the year data collection started) to 2018, the CHKD Sports Medicine PT program has administered over 23,000 iontophoresis with DSP treatments and none have resulted in a significant adverse reaction. Currently there are no published studies documenting this perceived clinical benefit and it is imperative to determine if it is better than the current home regimen. Outside of the benefits to the individual patient there are also benefits to the parent/ guardian of the minor child by minimizing their time lost from work. This in turn will have societal benefits (psychosocially and economically).

3 OBJECTIVES AND ENDPOINTS

PRIMARY OBJECTIVE:

To compare the functional outcomes of iontophoresis with DSP in combination with PT versus iontophoresis with placebo in combination with PT versus PT alone in pediatric patients diagnosed with apophysitis of the knee.

Primary Endpoints

- Length of time to meet RTS criteria as measured in days

Justification for Endpoints

- The ultimate goal of physical therapy treatment for knee apophysitis is to return children and adolescents to pain-free physical activity. The World Health Organization (WHO) recommends a minimum of 60 minutes a day of moderate to vigorous physical activity for school-aged children.[19] It is well documented that regular physical activity is essential for healthy growth and development by promoting cardiorespiratory and muscular fitness, as well as cardiovascular, metabolic, and bone health.[19] In addition to the vast physical benefits, regular physical activity also promotes psychological and social benefits.[19] The WHO reports that physically active children have been shown to demonstrate better academic performance and are suggested to be more apt to avoid drugs, alcohol, and tobacco.[19] Similarly, the risks of pediatric physical

inactivity are also well documented, and this inactivity in childhood can evolve into a lifetime of preventable comorbidities.[20] Currently, physical inactivity is the fourth leading risk factor for mortality.[20] Because the pain associated with knee apophysitis often results in a reduction in physical activity for the affected pediatric population, it is critical that they receive appropriate treatment to facilitate an expeditious return to pain-free return to physical activity for their physical, cognitive, and psychosocial well-being.

- The RTS criteria were developed to address pain-free, proper mechanics with common activities and movements to demonstrate patient readiness for safe RTS. The length of time to meet these criteria was selected as the specific endpoint to determine if one treatment produces faster resolution of symptoms. Expediting RTS has significant financial, physical, and psychosocial benefits. Decreasing the length of time for RTS will reduce the cost for rehabilitation by limiting the number of required PT visits. It will also reduce the negative physical, emotional, and social implications associated with the activity restrictions often imposed on patients with knee apophysitis.

SECONDARY OBJECTIVES:

To compare the patient reported outcomes of iontophoresis with DSP in combination with PT versus iontophoresis with placebo in combination with PT versus PT alone in pediatric patients diagnosed with apophysitis of the knee.

To compare the safety of iontophoresis with DSP in combination with PT versus iontophoresis with placebo in combination with PT versus PT treatment alone in pediatric patients diagnosed with apophysitis of the knee.

Secondary Endpoints

- Patient reported percent difficulty with activities as measured by the LEFS
- Patient reported pain as measured by the FACES Pain Scale
- Patient reported activity as measured by the Godin Leisure-Time Activity Questionnaire
- Safety as measured by number and intensity of iontophoresis or DSP-related adverse events

Justification for Endpoints

- The LEFS is a validated patient reported outcome tool that assesses the patient's ability to perform 20 different activities involving the lower extremity. It allows the patient to rate his/her level of difficulty with each task as a result of pain or impairments to the involved lower extremity. The LEFS was selected based on its ease of administration and its inclusion of both common Activities of Daily Living (ADL's) and more advanced sport-specific activities.
- The FACES Pain Scale allows the pediatric patient to select the face that best represents his/her pain intensity. This is assumed to generate a more accurate pain rating than a quantitative estimation required with a numerical rating scale, where children may not all have a good understanding of the quantitative value of numbers. It has been documented that children prefer the FACES Scale to the Visual Analog Scale, which would require them to select a point on a horizontal line to indicate pain intensity. Using the FACES Pain Scale will allow Treating Therapists to track the patients' subjective pain ratings throughout the rehabilitation process.
- The Godin Leisure-Time Activity Questionnaire is a patient reported outcome tool that quantifies the patient's level of strenuous, moderate, and mild physical activity in a typical week. This provides the Treating Therapists with quantitative information regarding the

patient's typical level of physical activity prior to the onset of knee apophysitis to facilitate a full return to prior level of function following completion of physical therapy. The Godin Leisure-Time Activity Questionnaire was selected based of its inclusion of low, moderate, and high level physical activities with examples for each category for ease of completion by patient/parent.

- Tracking the number and intensity of adverse events (see Section 8.3.3.1 Definition of Adverse Events) will determine if iontophoresis with DSP is a safe treatment option for this population by providing quantitative and qualitative data.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The primary study hypothesis is that the time to achieve RTS criteria for pediatric patients with apophysitis of the knee who receive iontophoresis with DSP treatment and PT will be different than those who receive placebo or PT alone. The secondary study hypotheses are: that the patient reported outcomes for pediatric patients with apophysitis of the knee who receive iontophoresis with DSP treatment and PT will be different than those who receive placebo or PT alone; and the frequency and intensity of adverse events among pediatric patients with apophysitis of the knee who receive iontophoresis with DSP treatment and PT will be different from those who receive placebo or PT alone.

This is a Phase II trial. It is a three-arm, randomized, double-blind, placebo-controlled comparison study looking at the functional and patient reported outcomes of iontophoresis (with DSP or placebo) in conjunction with PT versus PT alone to treat pediatric patients diagnosed with apophysitis of the knee.

The study is double-blinded and placebo-controlled to minimize bias. There will be three (3) study groups

- Iontophoresis using DSP (study drug) + PT
- Iontophoresis using placebo + PT
- PT alone

Participants in all three groups will receive the standard PT protocol for apophysitis of the knee. This will involve up to 20 visits. Participants randomized to the iontophoresis groups will receive up to 12 iontophoresis treatments over a maximum of eight (8) weeks. All participants will receive a phone follow-up call 30 days after they meet RTS criteria as well as an electronic survey follow-up 90 days after they meet RTS criteria.

This study will only be conducted through the Children's Hospital of the King's Daughters Sports Medicine PT Department with study-related activities occurring at six of CHKD's Hampton Roads PT clinics. All study-related activities will be completed by Physical Therapists and Physical Therapist Assistants (Treating Therapists) trained on the protocol and CITI trained.

Concomitant therapies, age, gender, and race will be conducted to analyze the possible effects of these covariates on length of time to RTS

Stratifications of age, gender, and race will be conducted to analyze the possible effect of these covariates on length of time to RTS as well as on patient reported outcomes LEFS, Godin Leisure-Time Activity, and FACES Pain Scale and on safety outcomes.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study is designed to compare the efficacy of iontophoresis with DSP as part of a comprehensive PT treatment. This will be compared to a placebo group receiving iontophoresis with placebo in combination with PT and to a third group receiving PT alone. The use of these control groups is proposed due to the high placebo effect observed in the pediatric population. It is proposed that in groups receiving iontophoresis, both subjects and Treating Therapists will be blinded to whether the patient is receiving DSP or placebo to minimize bias. Due to the fact that the third group is receiving only PT, it will be impossible for the subjects or Treating Therapists to be blinded to group assignment.

Because current literature on knee apophysitis treatment typically recommends Non-Steroidal Anti-Inflammatory Drugs (NSAID's), ice, rest, home exercises, bracing, and PT, the placebo group and the PT only group would still be receiving what is cited as appropriate treatment for the diagnosis. Therefore, there should be no ethical concerns with using a control group receiving iontophoresis with placebo or with a group receiving PT alone.

4.3 JUSTIFICATION FOR DOSE

DSP will be supplied as a 4 mg/ml concentration, with 1.5 ml of the solution used for each iontophoresis treatment per the labeling instructions and current standard of practice.

0.9% sodium chloride (placebo) will be supplied at a volume equal to that of the DSP to appear identical for blinding purposes.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The clinical trial is considered completed when the last participant's last scheduled study-related activity is completed.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Written approval from the referring physician for potential subject to be considered for enrollment into this study
2. Provision of signed and dated informed consent form
3. Stated willingness to comply with all study procedures and availability for the duration of the study
4. In good general health as evidenced by written approval from referring physician for potential inclusion in study.

5. Has the ability to effectively identify pain/burns and communicate with the investigators or their parents that they are experiencing pain or burning during treatment
6. Referred to CHKD Sports Medicine PT by CHKD Primary Care Sports Medicine physicians or CHKD Orthopedics physicians with a diagnosis of apophysitis of the knee and with a prescription for standard PT treatment with iontophoresis
7. Able and willing to complete iontophoresis treatments within eight (8) weeks of first treatment
8. Must be ambulatory
9. Males 7 to 14 years of age who have not reached skeletal maturity (skeletal maturity based on referring physician's clinical judgement or as demonstrated via radiograph images taken within 90 days of enrollment)
10. Females 7 to 14 years of age who have not reached skeletal maturity (skeletal maturity based on referring physician's clinical judgement or as demonstrated via radiograph images taken within 90 days of enrollment) and who meet one of the following criteria:
    a. Pre-menarcheal
    b. Within two (2) year post onset of menses
11. Males or females over the age of 14 only with radiographic evidence of skeletal immaturity, with images taken within 90 days of enrollment
12. Index knee symptomatic for pain with activities of daily living or while playing sports.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Index knee symptomatic for pain only with palpation and not with activities of daily living or while playing sport
2. Diagnosis of bilateral apophysitis of the knee where both knees meet all of the inclusion criteria
3. Systemic fungal infections
4. Has an implanted electronic device
5. Has a known sensitivity to DSP
6. Presence of damaged skin, denuded skin, or other recent scar tissue on index knee
7. Presence of active dermatologic conditions in the affected area (e.g., eczema, psoriasis)
8. Presence of an abnormal neurological exam that indicates the subject would have a reduced ability to perceive pain (e.g. peripheral neuropathy)
9. Has a known sensitivity to electrical current
10. Is currently taking systemic steroids
11. Has had iontophoresis with DSP treatment within the past 30 days
12. Previously enrolled in this study
13. Currently enrolled in another treatment research study

5.3 LIFESTYLE CONSIDERATIONS

As part of standard of care, patients will be provided instructions for icing, limiting physical activity, and taking NSAIDs and bracing their knee as recommended by their referring physician. Lifestyle considerations specific to this study, include:

- Adhere to the SoA (see Section 1.1.3 Schedule of Activities)
- Wear their patch for the full two (2) hours, then discard in a trashcan

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential subjects for this study will include patients referred to CHKD Sports Medicine PT by CHKD Primary Care Sports Medicine physicians or CHKD Orthopedic physicians with a diagnosis of apophysitis of the knee and with a prescription for standard PT treatment and iontophoresis. CHKD Primary Care Sports Medicine physicians and CHKD Orthopedic physicians may provide the patient and his/her family an informational flyer about the study and will be encouraged to contact the Principal Investigator if they are interested in learning more about it before their initial PT evaluation.

Given the natural course of apophysitis of the knee, this study population will involve children. All children ages 8 to 17 years old will give both verbal and written Assent as well as their parent/guardian providing written consent for those less than 18 years of age.

Based on the analysis plan, a total of approximately 49 subjects per group will be required, with a total enrollment of 147 subjects.

All potential subjects who are screened to participate in the study will be documented on a Screening Log.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention for this project is DSP administered via iontophoresis. Iontophoresis is a non-invasive delivery mechanism for transmitting a medication to a local area of the body. The I-Bresis™ System and I-Bresis™ Patch will be the delivery system utilized for this study. The I-Bresis™ System is indicated for the administration of soluble salts or other drugs into the body for medical purposes as an alternative to hypodermic injection. The I-Bresis™ System consists of three components: a Charging Station, a rechargeable Controller and a disposable Patch. The I-Bresis™ Patch is a disposable, single-use patch with a battery and current-limiting circuitry, and can deliver both negatively and positively charged water-soluble drug/compounds across intact skin. The I-Bresis™ System will be used in accordance with instructions for use.

- Device size(s) Patch: 13.5cm x 6.5cm that holds 1.5mL of fluid on each side of the patch
- Device model(s)
    - I-Bresis™ charging station: 1360
    - I-Bresis™ Controller: 1361
    - I-Bresis™ Patch: 5000060

- Description of each component
    - The I-Bresis™ charging station is a rectangular piece of equipment that has four charging ports to which I-Bresis™ Controller attaches. This device is plugged into a standard wall outlet for power. Each individual charging port has a light to signify if the device is charging (yellow) or fully charged (green).[21]
    - The I-Bresis™ Controller: 1361 is a small triangular device that attaches to the I-Bresis™ Patch. There are three buttons on top of the device: Power, Start/pause, and standard mode. There is a light on the front of the device that blinks when the device is powered on. The light is solid when the device is running.[22]
    - The I-Bresis™ Patch is a 13.5cm x6.5cm adhesive patch with two "patch drug pads", each of which are labeled with a polarity of either positive (+) or negative (-). Each drug pad holds ~1.5 ml of fluid. Approximately 1.5 ml of a water-soluble drug/solution is placed on one drug pad and approximately 1.5 ml of the saline solution (supplied in the I-Bresis™ Patch carton as single-use, sealed vials of sterile 0.9% saline solution) is placed on the other.[23]

- Device settings and programming : 3mA current for three (3) minutes then 0.67mA for 120 minutes
- Duration of exposure: 123 minutes (3 minutes of patch + controller, 120 minutes of patch only)
- Frequency of exposure : maximum twice per week for a total of 12 sessions over a maximum of eight (8) weeks

The I-Bresis™ System is commercially available and will be used in accordance with approved labeling.

The drug and solution administered via the iontophoresis patch will be DSP and 0.9% sodium chloride (placebo).

Dexamethasone sodium phosphate (DSP) is a synthetic adrenocortical steroid that has potent anti-inflammatory effects but lacks the sodium-retaining property of hydrocortisone. Corticosteroids inhibit multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage, and migration of inflammatory cells thereby suppressing inflammation. DSP 0.75 mg has anti-inflammatory activity equivalent to approximately 5 mg of prednisone, 25 mg of cortisone, and 20 mg of hydrocortisone. DSP is long-acting (half-life 200 minutes) and is recommended as adjunctive therapy in a variety of inflammatory disorders and as an immunosuppressant agent.[11]

0.9% Sodium Chloride injection: is a sterile, nonpyrogenic solution of sodium chloride in water for injection. The solution contains 9 grams/L sodium chloride, USP (NaCl), with 154 mEq/L sodium and 154 mEq/L chloride. The nominal pH of sodium chloride is 5.0 (4.5 to 7.0) and osmolarity is 308 mOsmol/L.[24]

6.1.2 DOSING AND ADMINISTRATION

The I-Bresis patch is designed to hold 1.5mL of fluid on each side (negative and positive) of the patch. DSP is supplied in 120 mg/30 mL (4 mg/1 mL) multidose vials, and will be repackaged into blinded bottles holding 1.8 mL (7.2 mg). 0.9% sodium chloride will be repackaged into blinded bottles holding 1.8 mL. Both DSP and 0.9% sodium chloride will be administered using the I-Bresis System.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

DSP injection and 0.9% sodium chloride injection will be supplied by the CHKD Pharmacy Department in identical looking single-use bottles, each containing 1.8 mL of solution and labeled in a blinded fashion as either Iontophoresis Study Drug “A” or “B”. These bottles will be provided by the pharmacy to the outpatient PT clinics and administered by the investigators to the patients. Trained site staff in the PT clinics will be responsible for accountability of the study drug, exercising accepted medical and pharmaceutical practices. Expired or unused study drug bottles will be returned to the CHKD Investigational Pharmacy and disposed of per the CHKD Pharmacy Investigational Drug Policy.

For all study bottles prepared, the CHKD Investigational Pharmacy will keep a compounding log to record the following information: date of preparation, manufacturer, lot number, manufacturer expiration date, number of bottles prepared, expiration date of the study bottles, and assigned numbers of the bottles. This compounding log will only be accessible to study pharmacists to ensure blinding is maintained.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

DSP Injection, USP 4 mg/mL (Fresenius Kabi USA, LLC) is a clear colorless solution of DSP in water for injection. DSP will be provided in individual empty bottles, each containing 1.8 mL (7.2 mg DSP). Each bottle will contain 1.5 mL (6 mg) DSP for study administration and 0.3 mL of overfill to account for loss during transfer. Each bottle will be labeled identically to the placebo with the label designating assigned bottle number, study drug “A” or “B” and the expiration date clearly marked on the label.

0.9% Sodium Chloride Injection, USP (Baxter Healthcare Corporation) is a clear colorless solution of sodium chloride in water for injection. The 0.9% sodium chloride solution will be provided in individual empty bottles, each containing 1.8 mL (no active drug). Each bottle will contain the 1.5 mL dose to be administered and 0.3 mL overfill to account for loss duringtransfer. Each bottle will be labeled identically to the DSP with the label designating assigned bottle number, study drug “A” or “B” and the expiration date clearly marked on the label.

6.2.3 PRODUCT STORAGE AND STABILITY

All bottles (study drug and placebo) will be stored in a secured space at each of the study sites. These bottles will be stored between 20° to 25°C (68° to 77°F), and will be protected from freezing and excessive heat. All bottles will have a shelf life of 30 days from transfer and the expiration date will be clearly marked on the label. All bottles will be protected from light.

Iontophoresis supplies, controlling stations, chargers, and patches will be stored in the outpatient clinics at room temperature per the device labeling instructions.

6.2.4 PREPARATION

DSP and 0.9% sodium chloride will be supplied by the CHKD Pharmacy Department in identical looking bottles, each containing 1.8 mL of solution and labeled in a blinded fashion as either Drug "A" or "B". Trained Therapists will be responsible for the preparation of the iontophoresis patches. Aseptic techniques will be utilized when preparing the patches. Upon randomizing a subject, the treating physical therapist will retrieve the appropriately labeled bottle ("A" or "B", based on the subject's randomization assignment) from the locked cabinet and check the expiration date. The treating physical therapist will apply 1.5 mL liquid (from the assigned bottle) to the negative side of the patch per the instructions listed in the I-Bresis Instruction for Use. The Therapist will then apply 1.5mL of 0.9% sodium chloride from the saline ampoules provided in the I-Bresis™ carton to the positive side of the patch and will then obtain two patient identifiers (ex. Full name, DOB) from the patient prior to patch application per clinic policy.

The treatment site will be cleaned thoroughly with alcohol prep (ensuring the area being treated is free from other creams and topical medications, including topical steroids) as described in the instructions listed in the I-Bresis Instructions for Use.[23] The negative side of the patch will be applied over the tibial tubercle in patients with OSD and over the inferior patellar pole in patients with SLJ.

The I-Bresis controller will be turned on then connected to the patch. At that time, the start button will be pressed and the current will be initiated at 3mA for an initial 3minutes of treatment. Following this three minutes, the controller will be removed and turned off. The Patch will remain in place and an 80 mA-minute dose will be applied over two hours. The therapist will ensure that the patch fully conforms to the patient and that it will maintain full contact with the skin. To improve adhesion of the patch, the therapist may lightly wrap the patch with Pre-Wrap and secure the end with tape, ensuring the tape is not being applied over the patch so as not to bind it.

Subjects will be monitored by their therapist for adverse events for 15 minutes after the patch is applied following the initial application and for an appropriate amount of time following all subsequent applications. Subjects will leave the PT clinic with the patch in place. The patch will be programed to deliver medication over a two-hour period, automatically switching off iontophoresis after the maximum dose has been administered. Subjects will be instructed to remove the patch 2 hours after it has been applied as leaving the patch on longer than the recommended time may increase the risk of skin irritation. Subjects will be instructed to wrap the patch in paper towels and discard the Patch in a receptacle out of reach of children and pets.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

A center-stratified randomization method will be used to maintain balance between treatment groups and centers. Equal number of participants per intervention will be considered to maximize study power. The CHKD Pharmacy Department will hold the randomization key and will prepare bottles of study drug and placebo (see Section 6.2.2 Formulation, Appearance, Packaging, and Labeling).

Treating therapists will assign randomization codes in chronological order as participants enroll in the study. Since the study drug and sodium chloride are identical in appearance, the Treating Therapists will

be blinded to study assignment. Those participants assigned to "Group C", or standard PT alone, will be unblinded to treatment as they will not receive iontophoresis.

In the case of an unexpected and serious adverse event in which knowing the study assignment is critical to the medical care of the participant, the CHKD pharmacist may release this information to the Independent Safety Monitor only, who may share this information with the treating physician.

Both the Treating Therapist and the participants assigned to one of the two iontophoresis groups will be blinded to study treatment. The DSP injection and 0.9% sodium chloride injection are clear, colorless liquids that will be supplied by the CHKD Pharmacy Department in identical looking single-use bottles. Each bottle will contain 1.8 mL of solution and will be labeled in a blinded fashion as either Iontophoresis Study Drug "A" or "B".

In this study, the Treating Therapists will also perform all physical therapy assessments. While having a separate group of "assessing therapists" and "treating therapists" minimizes bias even further than the current study design, combining their roles is preferred as it reduces error by minimizing the number of therapists involved, improves completion consistency of the RTS Criteria Checklist, and minimizes scheduling conflicts caused when trying to coordinate two therapist's schedules for every study visit conducted.

6.4 STUDY INTERVENTION COMPLIANCE

All participants will be asked to attend up to 12 Study Treatment Visits within an 8-week period. Compliance with this request will be documented by the primary Treating Therapist with assistance from front office staff. The Treating Therapist will review all active study participants at his/her site to ensure each participant attended the two scheduled visits. Any study participants who missed a visit will be contacted by the therapist within 24 hours of the missed visit to be counseled on the importance of maintaining the assigned visit schedule and to ascertain if the participant wishes to continue with the study, as described in section 7.3. Lost to Follow-Up.

Participants and/or parents will be asked to verbally confirm or describe compliance with their HEP, patch wear time (for those assigned to Groups A and B), icing recommendations, activity modifications, and bracing and NSAID use as recommended by their referring physician.

6.5 CONCOMITANT THERAPY

Concomitant therapy during this study to include:

- NSAIDs for pain as recommended by referring physician, if applicable
- Brace use as recommended by referring physician, if applicable
- Ice for pain per standard of care as described on handout provided to all patients

Patients and/or parents will be asked at the beginning of each PT treatment about use of the concomitant treatment options listed above. This will be documented by the treating physical therapist each visit. Each of these concomitant treatments may help reduce pain, but they will be recommended to participants across all three treatment groups, so it is feasible to analyze and distinguish independent effects of the study intervention compared to any potential effects from the concomitant therapies described above.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Iontophoresis will be discontinued at the earlier of the following time points:

- The participant meets the RTS criteria
- The participant has completed 12 iontophoresis patch applications
- The participant has been receiving iontophoresis treatment for 8 weeks
- The participant develops any medical condition for which full participation in PT (including, but not limited to iontophoresis) would be contraindicated
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Discontinuation from iontophoresis does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Brief physical exam of the affected knee
- Adverse event review and evaluation
- Concomitant medication review
- FACES Pain Scale
- RTS Checklist
- 30-day Phone Follow-up
- 90-day Survey Follow-up
- LEFS

Subjects who experience a relapse of pain after the Clinic Check Visit and prior to the 90-day Follow Up will not receive additional iontophoresis treatment as part of the study plan. Subjects who fall into this category will be treated with standard of care treatment as determined by the Treating Therapist or referring physician.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Early Termination Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits or has gone ten (10) days without treatment, whichever comes first, and is unable to be contacted by the study site staff. The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 24 hours of missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

As Standard of Care:

- All patients who are referred to the participating PT clinics with a diagnosis of apophysitis of the knee and a prescription for PT with iontophoresis will receive a PT Initial Evaluation (IE). Per department policy, the PT IE must take place within 90 days of referral date as indicated on the script.
    - The IE includes: review of demographics, medical history, medication regime, strength and balance tests, pain assessment, review of home exercise program, icing instructions, activity restrictions, and bracing and NSAID instructions as recommended by their referring physician.
- After the IE, and as part of standard of care, all participants, regardless of group assignment, will receive a standardized PT treatment progression provided by qualified therapists.
    - As standard of care, PT progression visits may include up to 19 visits
- Clinic Check Visit – Two (2) to three (3) business days after a participant is cleared for RTS, or has received treatment for eight (8) weeks, whichever is sooner, the participant will return to the

clinic for the Treating Therapist to confirm the participant remains pain free and able to meet the RTS criteria.

- Physical therapy progression visits to further fine tune mechanics, strength, and stretch may occur after this visit as part of their standard of care.

Study-related:
Study-related procedures will begin on the first PT Treatment Day, which may be the same day as the IE or at the next PT visit, but never before the Consent is signed. If subjects meet inclusion/exclusion criteria and the potential participant consents to participate at the Initial PT Evaluation Visit, the IE and Enrollment/Randomization Study Treatment Visit 1 visits may be combined.

The following procedures/evaluations will be obtained by the Treating Therapists:

- Lower Extremity Function Scale (LEFS) - (see Appendix 12.1) – a patient reported paper-based questionnaire that asks the patient to choose the level of difficulty of completing 20 different activities. Assessed at Study Treatment Visits 1, 5, 12/RTS Criteria Met Visit, and 30-day Follow Up. Note: the LEFS will be administered over the phone at the 30-day Follow-Up Visit.
- FACES Pain Scale - (see Appendix 12.2) – a patient reported paper-based questionnaire that asks the patient to choose the face that best represents the pain they are experiencing in their knee. Assessed at the end of each Study Treatment Visit and again at the end of the Clinic Check Visit.
- RTS Criteria Checklist - (see Appendix 12.3) – a paper-based checklist completed by the Treating Therapist to determine whether or not the participant is ready to safely return to sport. The checklist was created to include the basic movements typically required for sports activities, though these activities are also applicable for return to PE participation and free play, making it appropriate for all patients, even those not involved in organized sports. These movements include squatting, running, bilateral and unilateral jumping, back pedaling, and quick direction changes. The checklist includes qualifying criteria for proper mechanics and requires that all activities be pain-free. The checklist was created to assess readiness for sports participation without actually requiring that the patient return to sport participation to meet criteria, as not all patients participate in organized sports or are in-season year round. The items assessed as part of this checklist are all part of normal standard of care for physical therapy. Assessed at each Study Treatment Visit and again at the Clinic Check Visit.
- Godin Leisure-Time Exercise Questionnaire (see Appendix 12.4) – a paper-based subject self-reporting questionnaire comprised of four (4) items that address the amount of time an individual engages in mild, moderate, and strenuous leisure time physical activity of at least 15 minutes in duration during a typical week. Assessed at Study Treatment Visit 1 and at the 30-day phone follow-up (see Appendix 12.5 30-Day Phone Follow Up) and 90-Day Follow-Up (see appendix 12.6 90-Day Follow-Up – Electronic Survey).
- Study Treatment:
  - Iontophoresis (Groups A and B only) - ~ 3 minutes in clinic and 2 hours at home - The iontophoresis patch will be applied by a trained therapist in blinded fashion for all participants assigned to groups A and B (see section 6.1.2 Dosing and Administration). Performed at Study Treatment Visits 1 – 12 (Maximum of 12 treatments, maximum of 8 weeks since first Study Treatment Visit, or when RTS criteria are met and confirmed at the Clinic Visit Check, whichever is sooner).
  - For subjects assigned to Group “C” (PT only Group), Study Treatment Visits 1 – 12 (maximum of 8 weeks since first Study Treatment Visit, or when RTS criteria is met) will

include only their standard PT Treatment Visits: Study Treatment 1 = Standard PT Treatment 1, Study Treatment 2 = Standard PT Treatment 2….).

Note: Participants who initially meet RTS Criteria but fail to meet the RTS criteria when they return for their Clinic Visit Check will continue with their assigned study treatment until the sooner of: they once again achieve RTS criteria, they have received 12 study treatments, or they have received study treatment for eight (8) weeks.

8.2 SAFETY AND OTHER ASSESSMENTS

The following procedures/evaluations will be obtained by qualified Therapists treating the subjects*:*
Assessed At Enrollment/Randomization Study Treatment Visit 1*:*

- Inclusion/Exclusion Criteria - Based on the patient's medical history and review of the initial evaluation, the Treating Therapists will determine whether patients meet eligibility criteria for the study.
  Note: if radiograph images were obtained to determine skeletal maturity, the Treating Therapist will ensure the results are documented in the radiologist's notes or noted in the physician's notes in the electronic medical record.
- Informed Consent - Treating Therapist will conduct the informed consent process as outlined in Section 10.1.1.2 of this document.
- Randomization - After a patient signs Consent, the Treating Therapist will assign the patient to the research group per the randomization log at the Site (see section 6.3 Measures to Minimize Bias: Randomization and Blinding).

Assessed at All Study Treatment Visits:

- Brief Physical examination of the affected knee - an evaluation made by the treating physical therapist to include: skin color, temperature, presence of edema, turgor, pain with palpation/pressure, changes to skin texture, and integrity. Also assessed at Clinic Check visit.
- Concomitant Medication Review - a paper-based form completed by the Treating Therapist to document drug, dose, frequency, start and stop dates, and reason for taking. Also assessed at Clinic Visit Check visit.
- Adverse Event Evaluation - a paper-based form completed by the Treating Therapist to document occurrence, severity, relatedness, duration, and expectedness of the event. Subjects receiving iontophoresis will be specifically monitored for possible burns. This data will be captured during the examination of the affected knee as well as for 15 minutes post patch application.
  Also assessed at Clinic Visit Check visit, 30-Day Phone Follow Up and electronically at the 90-Day Follow Up (see Appendix 12.6 90-Day Follow Up – Electronic Survey)
- Compliance Checks – a paper-based form completed by the Treating Therapist to assess participant compliance with: study visits, length of time iontophoresis patch worn, home exercise program, icing, activity restriction, and bracing instructions. Also assessed at Clinic Check visit.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS AND SUSPECTED ADVERSE REACTION

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE) OR SERIOUS SUSPECTED ADVERSE REACTION

An AE or suspected adverse reaction is considered "serious" if, in the view of the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The Treating Therapists trained on this protocol will be responsible for classifying an AE. All AEs will be assessed for severity using the definitions below:

- Severity of Event (Intensity) – The following guidelines will be used to describe severity:
  - **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
  - **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
  - **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will have their relationship to study intervention assessed by the Treating Therapist who examined and evaluated the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The Treating Therapist who examined and evaluated the participant will be responsible for determining whether an AE or suspected adverse reaction is expected or unexpected. An AE or suspected adverse reaction will be considered unexpected if the nature, severity, or frequency of the event is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents (the IRB-approved research protocol and the current IRB-approved informed consent document), and (b) other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event. Whether or not the event is consistent with risk information described in the device package insert, drug package insert, or consent form.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or serious adverse event (SAE) may come to the attention of study personnel during study visits, during the 30-day follow up phone call or from the 90-day electronic survey. AEs will be assessed at each treatment visit through the performance of a brief physical exam, interview by the Treating Therapist, review of concomitant medications, as well as from patient-reported responses to the FACES Pain scale and LEFS (assessed only at Study Treatment Visit 1, 5, 12, and 30-day follow-up).

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a clinical assessment), expectedness, and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The treating Therapist will record all reportable events with start dates occurring any time after informed consent is obtained until 90 days after RTS criteria met or participant has received study treatment for eight (8) weeks, whichever is the shorter of the two time periods. At each study visit, the treating Therapist will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolved or deemed by PI and Independent Safety Monitor as chronic or stable.

8.3.5 ADVERSE EVENT REPORTING

The Treating Therapist will record all adverse events on an Adverse Event Log and will evaluate for seriousness, severity, expectedness, and relatedness. Adverse events that impact the safety of the subject or the ability of the subject to continue on with the study will be communicated immediately (within 24 hours) to the referring physician. On a monthly basis, the Principal Investigator will provide the Independent Safety Monitor cumulative AE reports. The Independent Safety Monitor, in consultation with a physician as needed, will monitor for accuracy and will have the authority to recommend continuation of the trial, modification to the trial, or termination of the trial in the event of unacceptable adverse events.

The Sponsor will notify all participating Investigators and the FDA (via an IND Safety Report) of any potential serious risks as soon as possible, but no later than 15 calendar days after the Sponsor determines that the information qualifies for reporting. Any adverse event not initially determined to be reportable but later determined to be reportable, will be submitted as an IND Safety report to the FDA as soon as possible, but no later than 15 calendar days after the determination is made.

The following AE reporting guidelines will be utilized in this protocol:

EVENT	REPORTED BY WHOM	TO WHOM (TIMEFRAME TO REPORT)
AE deemed *Serious* – see Section 8.3.6 Serious Adverse Event Reporting		
AE deemed *Not Serious*	Treating Therapist Principal Investigator	• Principal Investigator (provide in weekly AE Report) • Independent Safety Monitor (ISM) (provide in monthly AE Report)
AE deemed *Severe*	Treating Therapist Principal Investigator	• Principal Investigator – Immediately (within 24 hours of becoming aware of event) • Referring Physician –

		immediately (within 24 hours of becoming aware of event) • ISM - Immediately (within 24 hours of becoming aware of event)
AE deemed *Related*	Treating Therapist Principal Investigator	• Principal Investigator (provide in weekly AE Report) • ISM (provide in weekly AE Report)
AE deemed *Unexpected*	Treating Therapist Principal Investigator	• Principal Investigator – Immediately (within 24 hours of becoming aware of event) • Referring Physician – immediately (within 24 hours of becoming aware of event) • 1. ISM - Immediately (within 24 hours of becoming aware of event) • 2. Eastern Virginia Medical School (EVMS) Institutional Review Board (IRB) (immediately upon becoming aware of the event and in writing within five (5) business days) • 3. CHKD Hospital Research Coordination (HRC) (in writing within five (5) business days) • 4. All Investigators and FDA (IND Safety Report) (as soon as possible, but not later than 15 calendar days after the Sponsor determines the information qualifies for reporting) if **unexpected + serious**

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The treating Physical Therapist will record all serious adverse events on a Serious Adverse Event (SAE) Form. The following SAE reporting guidelines will be utilized in this protocol:

EVENT	REPORTED BY WHOM	TO WHOM (TIMEFRAME TO REPORT)
AE deemed *Serious*	Treating Therapist	• Principal Investigator – Immediately (within 24 hours of becoming aware of event) • Referring Physician – immediately (within 24 hours of becoming aware of event)
	Principal Investigator	• 1. ISM - Immediately (within 24 hours of becoming aware of event) if determined to meet criteria for unanticipated problem • 2. EVMS IRB (immediately upon becoming aware of the event and in writing within five (5) business days) if determined to meet criteria for unanticipated problem • 3. CHKD HRC (in writing within five (5) business days) if determined to meet criteria for unanticipated problem

The Principal Investigator is responsible for signing all SAE forms. All serious adverse events (SAEs) will be followed until satisfactory resolution or until the Principal Investigator, in coordination with the ISM, deems the event to be chronic or the participant is stable.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Should an AE occur in the study that affects the risks or possible willingness for participants to continue, the Site will provide all study participants with an IRB-approved letter of notification.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The Treating Therapist will record all unanticipated problems. The following UP reporting guidelines will be utilized in this protocol:

EVENT	REPORTED BY WHOM	TO WHOM (TIMEFRAME TO REPORT)
Unanticipated Problems	Treating Therapist Principal Investigator	• Principal Investigator – Immediately (within 24 hours of becoming aware of event) • 1. ISM - Immediately (within 24 hours of becoming aware of event) • 2. CHKD HRC (in writing within five (5) business days) • 3. EVMS IRB (immediately upon becoming aware of the event and in writing within five (5) business days)* • 4. Office of Human Research Protections (OHRP) with guidance from EVMS IRB and CHKD HRC

The UP report will include the following information:

- Name of the Institution conducting the research

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

*A follow-up or final report will follow by the earlier of 14 days or when an investigation has been completed or a corrective action plan has been implemented.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Should a UP occur in the study that affects the risks or possible willingness for participants to continue, the Site will contact all study participants, inform them of the new information, request that they come back to the clinic to discuss if deemed necessary, provide them with an IRB-approved letter of notification, and follow any instructions from the EVMS IRB regarding reconsenting or withdrawing from the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

  Length of time to meet RTS criteria as measured in days

  Null Hypothesis: Time to achieve RTS criteria for Pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT is the same as those who receive iontophoresis with placebo and PT or PT alone.

  Alternative Hypothesis: Time to achieve RTS criteria for Pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT will be different from those who receive iontophoresis with placebo and PT or PT alone.

- Secondary Endpoint(s):

  Efficacy: Patient reported outcomes:

  Null Hypothesis: There is not any significant difference in patient reported outcomes (LEFS, FACES pain scale, and Godin Leisure-Time Exercise) between pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT and those who receive iontophoresis with placebo and PT or PT alone.

  Alternative Hypothesis: Patient reported outcomes (LEFS, FACES pain scale, and Godin Leisure-Time Exercise) of pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT will be different from those who receive iontophoresis with placebo and or PT alone.

Safety: Frequency and intensity of adverse events

Null Hypothesis: There is not any significant difference in frequency and intensity of adverse events between pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT and those who receive iontophoresis with placebo and PT or PT alone.

Alternative Hypothesis: Frequency and intensity of adverse event among pediatric patients with apophysitis of the knee who receive iontophoresis with DSP and PT will be different from those who receive iontophoresis with placebo and PT or PT alone.

9.2 SAMPLE SIZE DETERMINATION

To assess the primary variable of interest, a power analysis indicated that a total sample of 126 participants would be required to detect medium effects ($f = 0.28$) with 80% power and $\alpha = 0.05$ using Generalized Linear Model (GLM).

The required sample size to test secondary hypotheses was calculated as 87 and 108 participants for patient reported outcomes and safety, respectively. Therefore, a total sample of 126 participants provides sufficient power for testing secondary hypotheses.

Given an estimated 15% non-compliance rate, the sample size will be increased by 15%, for a total sample size of 147 participants (49 per group).

9.3 POPULATIONS FOR ANALYSES

A Modified Intention-to-Treat Analysis Dataset will be utilized, so that participants who received at least one dose of study intervention will be included in the analysis dataset.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Continuous variables will be expressed as mean, standard deviation, median, and range. Categorical variables will be presented as frequency and percentage. All statistical tests will be two-sided and $p < 0.05$ will be considered as statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

A GLM will be conducted to test for significant difference in time to RTS (in days) between pediatric patients with apophysitis of the knee who receive iontophoresis with DSP treatment and PT and those

who receive placebo or PT alone. The result will be presented as average time to RTS with 95% confidence interval for intervention groups. Non-informative censoring will be checked to ensure mechanism of censoring is independent of treatment groups.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

A Generalized Estimation Equation (GEE) Model, including baseline records, will be used to check for changes in LEFS, FACES pain scale, and Godin Leisure-Time Exercise between treatment groups over time. Results for LEFS and Godin Leisure-Time Exercise will be presented as mean with 95% confidence interval, and results for FACES pain scale will be reported as odds ratio and 95% confidence interval.

9.4.4 SAFETY ANALYSES

A GEE model will be conducted to estimate likelihood of occurring and intensity of adverse events for Pediatric patients with apophysitis of the knee who receive iontophoresis with DSP treatment and PT as compared to those who receive placebo or PT alone.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Age at admission and baseline patient reported outcomes will be compared between treatment groups using Analysis of Variance (ANOVA) test. Chi-square test will be conducted to test comparability of intervention groups in terms of gender and race distribution. Continuous variables will be presented as mean and standard deviation. Categorical variables will be expressed as frequency and percentage. All tests will be two-sided and $p < 0.05$ will be considered statistically significant.

9.4.6 SUB-GROUP ANALYSES

A Generalized Linear Model (GLM), including concomitant therapies, age, gender, and race will be conducted to analyze the possible effect of these covariates on length of time to RTS outcomes.

Generalized Estimation Equation model including concomitant therapies, age, gender, and race will be conducted to assess the effect of these covariates on LEFS, FACES, Godin Leisure-Time Exercise, and safety outcomes.

9.4.7 INTERIM ANALYSES

While recruitment is ongoing, interim results will be supplied, in strict confidence, to the ISM as frequently as requested. All individuals involved in the interim analyses, including the biostatistician, will be blinded to intervention assignment.

Interim analysis of the study will be conducted based on the alpha spending rule .[26] The proportion of the observed sample size (number of patients observed divided by the target sample size) will be considered as the information statistics. The p-value will be adjusted to maintain the overall study power of 0.05, two-sided.

The ISM will inform the PI of the results only if the test statistics exceeds the adjusted p-value in the primary efficacy or safety outcome and if, in the opinion of the ISM, the study should be considered for early termination. The study would not be terminated early if the difference is found only in a secondary outcome of efficacy, the p-value is smaller but close to the adjusted p-value, or when the variance is small. The decision to terminate the study early would be made by the ISM with consultation of a non-treating physician as needed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed either in written form in the participant's chart or directly into the electronic medical record. The following consent materials are submitted with this protocol:

- Informational Flyer - this flyer describes the basics of the study and contact information of the PI. This flyer serves as a means of providing the potential participant and their parent general information to review prior to their first visit with the physical therapist. This flyer will be available in the office settings of the CHKD Primary Care Sports Medicine physician's offices and CHKD Orthopedic Surgeon's offices.
- Patient Informed Consent Form
- Assent Form

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Patients seen by CHKD Primary Care Sports Medicine physicians or CHKD Orthopedic physicians with a diagnosis of apophysitis of the knee and referred to CHKD PT for PT treatment and iontophoresis treatment will be potential subjects for the study. The referring physician will provide written approval to the Treating Therapist that the patient may be considered for enrollment into this study. The referring physician may provide an IRB-approved Informational Flyer to the parent and child for their review prior to meeting with the Physical Therapist. The Principal Investigator's (PI) contact information will be provided on the Informational Flyer. Parents may choose to call the PI to discuss the study or request that the informational packet be emailed or mailed to them in advance of their IE Visit.

As standard of care, all patients referred for PT treatment and iontophoresis receive an IE in one of the CHKD PT clinics. After the Treating Therapist receives the referral and prior to the IE, the Treating Therapist will ensure the referring physician has provided written approval for the patient to be

considered for enrollment in the study. Once approval is secured, the Treating Therapist may contact the parent to discuss the study and answer any questions they may have. At the IE, the Treating Therapist will discuss the study with the patient and his/her parent/legally authorized representative (LAR) in detail and if interested in participating in the study, will provide them a copy of the IRB-approved informed consent and assent forms for review.

Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients will have the option to sign Consent on the day of the IE or take more time to consider it and decide at the beginning of their next Standard PT Treatment visit.

Informed consent will only occur at the PT clinics and will be conducted by the Treating Therapists who have been CITI trained. The Informed consent process will be initiated prior to the individual's agreeing to participate in the study and will continue throughout the individual's study participation. No study-specific procedures will be conducted until the Consent and Assent Forms are signed and dated.

Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records and the original scanned into the medical record and then stored in a locked office with the other essential documents of the study. The informed consent process will be conducted and documented in the source document. Participants who turn 18 years old or are emancipated during the course of the study will be re-consented.

The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the Principal Investigator to the Study Team, study participants, the EVMS IRB, and the CHKD HRC. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, and their staff. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the regulations, the reviewing IRB, and institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be maintained in REDCap per institutional policy. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Independent Safety Monitor**
Dana Reesman, PT, DPT CHKD Sports Medicine PT	Christopher Bertani, PT, DPT, MS, OCS, SCS, CSCS CHKD Sports Medicine PT
CHKD	CHKD
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Sub-Investigators:

Joel Brenner, MD, MPH – CSG Primary Care Sports Medicine
David Smith, MD – CSG Primary Care Sports Medicine
Beth Ackerman, PT, DPT, SCS – CHKD Sports Medicine PT
Christopher Bertani, PT, DPT, MS, OCS, SCS, CSCS – CHKD Sports Medicine PT
Ashley Koto, PT, DPT, ATC CHKD Sports Medicine PT
Alexandra McVicker, PT, DPT, OCS CHKD Sports Medicine PT
Tyler Miller, LPTA, CSCS, CES CHKD Sports Medicine PT
Lauren Pierce, PT, DPT, ATC CHKD Sports Medicine PT
Sara Stites, PT, DPT, ATC CHKD Sports Medicine PT

Alyssa Tieber, PT, DPT, ATC CHKD Sports Medicine PT
Christina Hellauer, PharmD – CHKD Pharmacy

10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of an ISM, an individual with the education, skills, and relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events with follow-up through resolution. The ISM, in consultation with a physician as needed, will evaluate individual and cumulative participant data when making recommendations regarding the continuation of the trial, modification to the trial, or termination of the trial in the event of unacceptable adverse events.

10.1.6 CLINICAL MONITORING

Internal site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), and with applicable regulatory requirements.

- On-site monitoring of this trial will be performed by qualified individuals within the CHKD Sports Medicine Team who have not participated in the enrollment or treatment of participants in this study. Monitoring will consist of 100% review of consent forms, inclusion/exclusion criteria, and RTS Checklist, and random review of remaining data points. A Monitoring Report will be provided to the Treating Therapist with a copy to the PI.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

All Treating Therapists will perform internal quality management of their own data collection, documentation and completion. The Treating Therapists will be responsible for correcting errors found by the Monitor.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks on the database will be generated. Any missing data or data anomalies will be communicated to the appropriate Treating Therapists for clarification/resolution.

The monitor will verify that the clinical trial is conducted and data are collected, documented (recorded), and reported in compliance with the protocol and applicable regulatory requirements.

The CHKD Investigational Pharmacist will monitor the Drug Accountability Logs for drug accountability. Any errors found will be corrected by the Treating Therapist.

All Treating Therapists will undergo site-specific protocol training as well training on obtaining and documenting Informed Consent and Good Documentation Principles. All Treating Therapists will

participate in training sessions conducted by the PI on adverse events (identifying, assessing, documenting, and reporting), the PT exercise protocol, Y balance testing, quad strength testing with hand-held dynamometer, iontophoresis patch preparation and application, administration of the patient-reported outcome measures (FACES Pain Scale and Godin Leisure-Time Activity Questionnaire), administration of the LEFS, and the RTS checklist. These sessions will include instructional handouts, demonstrations, and practice sessions to ensure good intra- and inter-examiner reliability.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the Treating Therapists at the site under the supervision of the Principal Investigator. Treating Therapists will follow “Good Documentation Principles” when completing study related documentation. These principles will ensure data are: attributable, legible, contemporaneous, original, accurate, enduring, available and accessible, complete, consistent, credible, and corroborated.

Source data may take the form of hardcopy worksheets or electronic data, obtained from the participant’s electronic medical record or paper chart, or through a REDCap survey. Per the CHKD Policy C1107 “Approval of Research”, a copy of the signed Informed Consent will be scanned into the participant’s electronic medical record. The treating physical therapist obtaining informed consent will place a consent note in the participant’s paper chart as well as scan a copy into the electronic medical record.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. The 30-Day Phone Follow Up Visits will be conducted by the Treating Therapist via a phone call to the participants and data obtained will be documented directly onto a visit worksheet. 90-Day Follow-Up Visits will be administered as REDCap surveys sent to the participant’s email or cell phone with phone follow up as needed for new adverse events identified or new medications identified that may be associated with an adverse event.

All original source documents for a single participant will be collected from the treating PT clinic, following CHKD’s Policy C3400.1 Transporting Protected Health Information, and transported and stored in the research office in a locked and secure cabinet.

All study-related clinical data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study-related documents will be retained per the CHKD record retention policy.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or regulatory requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It is the responsibility of the Treating Therapists to use continuous vigilance to identify and report deviations within two (2) working days of identification of the protocol deviation to the Principal Investigator. All deviations will be documented in study source documents. Protocol deviations that result in a change to the risk/benefit ratio or affect the integrity of the study will be reported to the EVMS IRB per their SOPs.[25]

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Naming of authors and contributors to publications resulting from this research project will be determined in line with the International Committee of Medical Journal Editors' (ICMJE) recommendations.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. None of the persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial have a conflict of interest. Should one develop, or be perceived to be present, it will be managed by following the CHKD Human Subjects Research – Conflict of Interest Policy C1108 and the EVMS IRB Conflict of Interest Policies.[25]

10.2 ABBREVIATIONS

ADLs	Activities of Daily Living
AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CHKD	Children's Hospital of the King's Daughters
CITI	Collaborative Institutional Training Initiative
CMP	Clinical Monitoring Plan

CRF	Case Report Form
DHHS	Department of Health and Human Services
DSP	Dexamethasone Sodium Phosphate
eCRF	Electronic Case Report Forms
FACES	Wong Baker Faces Pain Scale
FDA	Food and Drug Administration
GEE	Generalized Estimation Equation
GLM	Generalized Linear Model
HEP	Home Exercise Program
HIPAA	Health Insurance Portability and Accountability Act
HRC	Hospital Research Coordination
ICMJE	International Committee of Medical Journal Editors
IE	Initial Evaluation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LAR	Legally Authorized Representative
LEFS	Lower Extremity Function Scale
OHRP	Office for Human Research Protections
OSD	Osgood Schlatter Disease
PI	Principal Investigator
PT	Physical Therapy
QA	Quality Assurance
QC	Quality Control
RTS	Return To Sport
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SLJ	Sinding-Larsen-Johansson
SM	Sports Medicine
SoA	Schedule of Activities
UP	Unanticipated Problem

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	2018_08_27	Added IND#; Added language regarding potential burns; Revised inclusion criteria; Revised exclusion criteria; Revised preparation of study treatment; Added burn-specific AE monitoring and post-patch application AE monitoring; Added language regarding IND Safety Reporting; Clarified "Pain free" criteria for RTS; Added additional adverse event reporting requirements	
3.0	2018_09_18	Clarified data handling of 90-day electronic survey and added actual 90-Day Follow Up REDCap Survey	
4.0	2019_07_11	Lowered inclusion age to 7; added two study sites; raised estimated time to meet study enrollment; added email reminders	
5.0	2019_08_15	Added language differentiating between first time patch application monitoring and subsequent patch application monitoring.	
6.0	2020_05_20	Added language for conducting interim analyses; removed two (2) Investigators who left the organization.	

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12 APPENDICES

12.1 LOWER EXTREMITY FUNCTIONAL SCALE (LEFS)

Lower Extremity Functional Index

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem for which you are currently seeking attention. Please provide an answer for each activity.

Today, do you or would you have any difficulty at all with:

(Circle one number on each line)

Activities	Extreme Difficulty or unable to perform activity	Quite a bit of difficulty	Moderate difficulty	A little bit of difficulty	No difficulty
a. Any of your usual work, housework or school activities.	0	1	2	3	4
b. Your usual hobbies, recreational or sporting activities	0	1	2	3	4
c. Getting into or out of the bath.	0	1	2	3	4
d. Walking between rooms.	0	1	2	3	4
e. Putting on your shoes or socks.	0	1	2	3	4
f. Squatting.	0	1	2	3	4
g. Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
h. Performing light activities around your home.	0	1	2	3	4
i. Performing heavy activities around your home.	0	1	2	3	4
j. Getting into or out of a car.	0	1	2	3	4
k. Walking 2 blocks.	0	1	2	3	4
l. Walking a mile.	0	1	2	3	4
m. Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
n. Standing for 1 hour.	0	1	2	3	4
o. Sitting for 1 hour.	0	1	2	3	4
p. Running on even ground.	0	1	2	3	4
q. Running on uneven ground.	0	1	2	3	4
r. Making sharp turns while running fast.	0	1	2	3	4
s. Hopping.	0	1	2	3	4
t. Rolling over in bed.	0	1	2	3	4
COLUMN TOTALS					

Score variation ± 6 LEFTS points
MDC & MCID = 9 LEFS points

Score _____/80

12.2 WONG BAKER FACES PAIN SCALE

12.3 RETURN TO SPORT CHECKLIST

Phase 1 - Nonimpact

☐Pain-free ADL's

☐Squats x 10 pain-free with proper mechanics (all of the following must be met:)

- ☐No anterior tibial translation
- ☐Heels stay in contact with the ground
- ☐Neutral/slight external rotation foot placement
- ☐Knee stays in line with 2nd toe
- ☐Trunk upright
- ☐No trunk shift

NOTE: Must meet both Phase 1 criteria before progressing to Phase 2 criteria. Phase 2 criteria must be assessed/completed in the order listed below.

Phase 2 - Impact

☐Broad jumps x10 pain-free with proper mechanics (all of the following must be met:)

- ☐Knee in line with 2nd toe on take-off and landing
- ☐No anterior tibial translation on landing
- ☐Even footing on take-off and landing
- ☐Soft landing
- ☐Pain free

☐Single leg triple hop for distance (all of the following must be met:)

- ☐Met all above criteria for broad jumping
- ☐No loss of balance
- ☐No extra hop on landing
- ☐No touching down of either the contralateral lower extremity or the upper extremity
- ☐Stick and hold final landing for at least 3 seconds
- ☐Affected lower extremity within 85% of the unaffected lower extremity
- ☐Pain-free

☐ Modified T-test

- ☐Met all above criteria for single leg triple hop for distance
- ☐100% effort
- ☐Pain-free

12.4 GODIN LEISURE-TIME EXERCISE QUESTIONNAIRE

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) MILD EXERCISE (MINIMAL EFFORT) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. ☐	2. ☐	3. ☐

12.5 30-DAY PHONE FOLLOW UP

The treating therapist may choose to send the subject's guardian a reminder email prior to the 30-day phone follow-up to confirm date, time, and number to call, as well as to remind the subject to complete the LEFS and GLTAQ prior to the call. An electronic copy of the LEFS and GLTAQ will be included in the email in case the subject misplaced their copy provided at the Clinic Visit Check.

The following information will be gathered at the 30-day phone follow-up call:

Date of Call:

Adverse Events

Ongoing: Review Adverse Event Log to determine if there were any unresolved AEs from last clinic visit.

If yes, ask about AE to determine whether severity changed, if AE resolved, or if any new intervention was required.

Complete AE Log

New: Question: Since your last clinic visit, have you been seen by a doctor or had any new medical problems?

If yes, complete entry on AE Log

Concomitant Medications

Ongoing: Review current medications to confirm no change to drug, dose, and frequency

New: Question: Since your last clinic visit, have you started any new medications?

If yes, document drug, date started, reason for taking (if an AE, complete entry on AE Log), dose, frequency

Administer the LEFS

Administer the Godin Leisure-Time Activity Questionnaire

12.6 90-DAY FOLLOW UP (ELECTRONIC SURVEY)

Confidential

90-Day Follow Up

Please complete the survey below.

Thank you!

First Name _____

Last Name _____

Today's date _____

GODIN LEISURE-TIME EXERCISE QUESTIONNAIRE

1. During a typical 7-Day period (a week), how many times on the average do you do the following kinds of exercise for more than 15 minutes during your free time.

a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling) _____ (Times Per Week)

b) MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing) _____ (Times Per Week)

c) MILD EXERCISE (MINIMAL EFFORT) (e.g. yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking) _____ (Times Per Week)

2. During a typical 7-Day period (a week), in your leisure time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

- ◯ 1. OFTEN
- ◯ 2. SOMETIMES
- ◯ 3. NEVER/RARELY

Did you have any ongoing medical problems at your 30-day Follow Up call?

- ◯ Yes
- ◯ No

What is the ongoing medical problem? _____

Has this medical problem gone away?

- ◯ Yes
- ◯ No

What date did this medical problem go away? _____

Your physical therapist will be calling you to follow up on the medical problem. Please provide the best phone number for us to reach you. _____

Since your 30-day follow up call, have you been seen by a doctor or had any new medical problem?

- ◯ Yes
- ◯ No

Confidential

Your physical therapist will be calling you to follow up on the medical problem. Please provide the best phone number for us to reach you. _____

Since your 30-day Follow Up call, have you started any new medications?
- ○ Yes
- ○ No

What is the name of your new medication? _____

Please explain why you are taking this new medication (for example, "It is because I have a cold")? _____

Your physical therapist may call you to follow up on the new medications you are taking. Please provide the best phone number for us to reach you. _____