DF/HCC Protocol #: 19-579

TITLE: Preventative Skin Care for Children Undergoing Targeted Therapy **for CNS and PNS Tumors**

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SCHEMA

Prospective, Single-Arm Trial

Diseases: *CNS or PNS tumor* *Skin reactions to Targeted BRAF, MEK or pan-RAF inhibitor therapy* *Treatments:* *Preventative Skin care routine (PSCR) + dilute bleach baths*	CNS or PNS tumor + treatment with targeted BRAF or MEK Or pan-RAF Inhibitor (8 participants)

→ *Preventative skin care routine + dilute bleach baths*

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1. OBJECTIVES

Objective #1. To describe the proportion of children with cutaneous reactions to targeted BRAF, MEK, and Pan-RAF inhibitor therapies of a cohort receiving a daily preventative skin care regimen (PSCR) including sun protection, gentle skin care and every other day dilute bleach baths at 6 and 12 weeks.

Objective #2. To describe the number of different cutaneous reactions to targeted BRAF, MEK, and Pan-RAF inhibitor therapies per patient in children receiving daily PSCR including sun protection, gentle skin care and every other day dilute bleach baths at 6 and 12 weeks.

Objective #3. To describe the severity of cutaneous reactions to targeted BRAF, MEK, and Pan-RAF inhibitor therapies for children receiving PSCR including sun protection, gentle skin care and every other day dilute bleach baths at 6 and 12 weeks. using the following severity scales: Common Terminology Criteria for Adverse Events (CTCAE), Overall Dry Skin Score (ODS), Hand-Foot Skin Reaction and Quality of Life Score (HFS-14), Pediatric Quality of Life Inventory (PedsQL), and Children's Dermatology Life Quality Index (CDLQI).

1.1 Study Design

This prospective, single-arm phase 2 clinical trial will be performed at Dana-Farber Cancer Institute/Boston Children's Hospital***. Additional external sites will conduct the same study concurrently. Data from all sites will be pooled at the end of the study and a meta-analysis of all aggregated data will be performed. IRB approval will be obtained prior to initiation of the study. This study will include patients receiving MEK inhibitor, BRAF inhibitor or pan-RAF inhibitor therapies for CNS and PNS tumors. At this time, we do not have the personnel or funding required to coordinate with multiple departments to identify all patients receiving these therapies.

Baseline data will be obtained from each participant via medical record review, if applicable. Baseline data includes, but is not limited to the following: general demographic data (age at tumor diagnosis, gender, race), type of primary tumor, type of therapy regimen (targeted therapy agents/dose/duration, chemotherapy agents/dose/duration, radiation field location/size/dose), past and current immunosuppressive medications, secondary malignancies including melanoma and nonmelanoma skin cancer, and family history of skin diseases.

All patients will undergo skin examinations at the initial study visit, mid-study visit (6 weeks (+/- 2 weeks)), and at 12 weeks after treatment initiation. Weight-based dosing of MEK, BRAF, or Pan-RAF inhibitor therapies will be recorded at each visit. If any skin findings are present, patients and families will be asked about the timing, frequency, location and severity of these skin findings.

Patients will undergo a full mucocutaneous physical examination including skin, mucous membranes, hair, and nails during their dermatology visit. Abnormalities will be carefully documented, including degree of involvement (% body surface area, number of nails, % of scalp).

Patients receiving targeted therapy will be evaluated specifically for the following skin reactions, previously reported in the literature: follicular skin rash, acneiform skin eruption, cheilitis, xerosis, hand foot syndrome, eruptive nevi (defined as > 5 new nevi over a 3 month period), keratoacanthoma, squamous cell carcinoma, photosensitivity. Undefined skin reactions will also be recorded.

No biopsies will be performed for research purposes. Patients who do not have a scheduled Dermatology visit, but have concerning findings on skin exam, will be scheduled for a complete dermatology evaluation, where any biopsies would be conducted as clinically indicated as part of routine dermatologic care.

2. BACKGROUND

2.1 Study Disease(s)

A recent study by Song et al. shows that cutaneous reactions are common in children receiving targeted anti-cancer therapies for CNS tumors.[5] Anti-cancer therapies for children with CNS tumors include BRAF inhibitors (dabrafenib, vemurafenib, encorafenib) and MEK inhibitors (refametinib, trametinib, selunetinib, comibetinib). Cutaneous reactions occurred in 96% of the 22 patients enrolled in this study and included xerosis, follicular eruptions, photosensitivity, hand-foot syndrome, eruptive nevi, nail changes, paronychia and alopecia. While most reactions are not life threatening, cancer therapy is frequently discontinued due to factors including intolerable discomfort (pain, itching) and/or concern regarding one's appearance.[6] MEK inhibitors have also been approved for NF-related plexiform neurofibromas, with a similar cutaneous reaction profile.[21]

Given the high incidence of cutaneous reactions to targeted tumor therapy, preventative measures to decrease the incidence or severity of reactions should be considered. The most common reactions are a result of dry skin and sun exposure; thus it is plausible that a simple preventative skin care regimen that addresses gentle skin care and sun protection would be beneficial. In addition, follicular reactions and paronychia may be ameliorated by regular use of dilute bleach baths, which have been shown to decrease severity of atopic dermatitis in children and to decrease inflammation by down-regulating the NF-kappaB pathway.[7-9]

Compelling in vitro and in vivo data suggests that topical hypochlorite solution markedly blocks NFκB signaling.[9] Furthermore, Leung et al demonstrated that topical hypochlorite inhibits the expression of NFκB-dependent genes, and decreased incidence and severity of cutaneous reactions to anti-cancer therapy in a mouse model.[9] The concentrations of hypochlorite used therein mirrored those determined to be safe and efficacious in dilute bleach baths used in the treatment of atopic dermatitis in children.[10] Emerging literature in atopic dermatitis suggests that the mechanism by which dilute bleach baths improves skin disease is not antimicrobial,[11] but rather, anti-inflammatory.

Bleach is an inexpensive and widely available topical agent; its use in swimming pools, medical clinics and commercially available cleansers speak to minimal toxicity (in dilute concentrations)

in humans. Our aim is to determine if dilute bleach baths can attenuate the incidence and severity of reactions to targeted anti-cancer therapies. A study by Huang et al. surrounding dilute bleach baths for atopic dermatitis included children as young as 6 months of age and showed that patients treated with dilute bleach baths had significantly improved eczema severity[10].

Cutaneous effects of targeted therapies

Over the last decade, our knowledge of the molecular composition of pediatric CNS tumors has increased dramatically.[12] In turn, tumor specific "targeted" therapies are being developed and utilized at an incredible pace. Given the shared neuroectodermal origin of the brain and skin, the advent of these therapies has introduced new and important skin reactions, including the development of nevi and skin cancer during active treatment. Other associated skin reactions include xerosis, hand foot syndrome, follicular skin eruptions, and scalp pruritus or burning. These reactions can be severe enough to require discontinuation or modification of therapy. There is also evidence in adults receiving targeted cancer therapies that presence of cutaneous reactions can be a good prognostic sign.

A recent study was performed by Song et al. at Boston Children's Hospital under DFCI protocol # 15-541[5]. In this cross-sectional study, patients younger than 21 years of age receiving BRAF, MEK, and mTOR inhibitor monotherapy for a CNS tumor were enrolled over a one-year period. Full body skin examination, photographs of dermatologic findings, and initial treatment recommendations were included at the initial visit, and follow-up skin examinations were recommended every three months. Twenty-two patients were enrolled in the study. Ninety-six percent (21/22) of all patients had at least one skin reaction. The most common reactions across treatment groups included follicular/acneiform eruptions and xerosis. Two patients on MEK inhibitors and one patient on a BRAF inhibitor required therapy cessation due to severe cutaneous reactions[5].

Severity Scores

In order to assess the severity of cutaneous reactions to BRAF, MEK and pan-RAF therapies, we will use the following scores: the Common Terminology Criteria for Adverse Events (CTCAE), severity of xerosis measured by the Overall Dry Skin Score (ODS), severity of hand foot syndrome measured by the Hand-Foot Skin Reaction and Quality of Life Score (HFS-14), Pediatric Quality of Life Inventory General Well-Being Scale (PedsQL), and the Children's Dermatology Life Quality Index (CDLQI).

The Overall Dry Skin Score (ODS) is a clinical assessment of the presence and severity of skin dryness using a five- point scale. A score of '0' indicates no skin dryness, whereas a score of '4' indicates advanced skin roughness, large scales, inflammation and cracks. This score has been used in studies assessing skin dryness in nursing homes and pharmacies.[13] The Common Terminology Criteria for Adverse Events (CTCAE) has a standardized grading system for adverse events including cutaneous reactions to anti-cancer therapies that is validated and widely used in oncology[14]. Higher grades of cutaneous reactions have significant impact on quality of life and can lead to interruptions in cancer treatment.
The Hand-Foot Skin Reaction and Quality of Life Score (HFS-14) is a scale that has been

specifically developed and tested for patients with Hand-Foot Syndrome, which has been reported as a symptom of targeted cancer therapies. The HFS-14 questionnaire was developed using standardized methodology for QoL questionnaire development, which consisted of the following steps: gathering patient input, generating an exhaustive list of items, reducing the list of items, allocating items to domains, pilot testing, calculation of scores, and validation. A working group of experts including oncologists, a dermatologist, a public health physician, and health professionals having a good knowledge of HFS and day-to-day experience in the management of this condition was constructed for the development of this questionnaire.[15] The PedsQL is based on a modular approach to measuring HRQOL and consists of a 15-item core measure of global HRQOL and eight supplemental modules assessing specific symptom or treatment domains. The PedsQL was empirically derived from data collected from 291 pediatric cancer patients and their parents at various stages of treatment.[16] The Children's Dermatology Life Quality Index (CDLQI) is the most widely used instrument for measuring the impact of skin disease on quality of life (QoL) in children.[17] (Olsen, 2016).

Gaps in care

While cutaneous reactions to targeted therapies are common and can be dose or treatment limiting, no guidelines surrounding management of these reactions currently exists. It is imperative for pediatric dermatologists to be involved in not only managing individual patients with these reactions, but also in developing protocols that assist oncologists in managing this population as a whole.

In a recent retrospective study of 39 adult patients who experienced cutaneous reactions to anti-cancer therapy, 5 experienced dose interruptions, and one patient discontinued therapy altogether due to severe papulosquamous rashes.[18] In our experience, it is not uncommon for children to have treatment discontinuation due to skin rashes or reactions that are physically or emotionally bothersome for them. In their study, Song et al. propose an algorithm for treatment of common reactions, including basic skin care guidelines. However, no studies have investigated the efficacy of therapeutic or preventative measures.

The current skin care guidelines according to the National Cancer Institute are vague and not specific for different types of cancer or pediatric versus adult patients. The guidelines recommend using mild soaps and lotions, avoiding heating pads and ice packs, shaving less often, and using sunscreen and sun-protective clothing. For dry, itchy skin in reaction to cancer treatments, these guidelines recommend the following: “Avoid products with alcohol or perfume, which can dry or irritate your skin. Take short showers or baths in lukewarm, not hot, water. Put on lotion after drying off from a shower, while your skin is still slightly damp. Keep your home cool and humid. Eat a healthy diet and drink plenty of fluids to help keep your skin moist and healthy. Applying a cool washcloth or ice to the affected area may also help. Acupuncture also helps some people.”[19]

In addition, while there is data showing that pediatric brain tumor survivors suffer from a lower quality of life than healthy peers and even other childhood cancer survivors, there is no scientific literature that specifically addresses how cutaneous reactions to targeted anti-cancer therapy impact quality of life for these patients.[20] Because of the high incidence of cutaneous reactions to

MEK and BRAF inhibitor therapy, more data is needed on how cutaneous reactions to anti-tumor therapy impact quality of life for these patients.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

- Diagnosed with a CNS or PNS tumor between ages 6 months old -18 years old and will undergo treatment with at least one of the following:
    1. Targeted BRAF inhibitor therapy to treat the tumor
    2. Targeted MEK inhibitor therapy to treat the tumor
    3. Targeted pan-RAF inhibitor therapy to treat the tumor
- Patients must enroll in this trial prior to starting targeted therapy
- Subjects may participate in other studies, including therapeutic trials.
- Ability to comply with PSCR including sun protection, gentle skin care and every other day dilute bleach baths.
- Ability to understand and/or the willingness of their parent or legally authorized representative to sign a written informed consent document.

3.2 Exclusion Criteria

- Diagnosed with CNS or PNS tumor at > 18 years old
- No data in medical records regarding treatment exposures
- Treated with a BRAF, MEK or pan-RAF inhibitor in the last three months
- Past or present allergic reaction to bleach
- Past or present allergic reactions to sunscreen and/or creams, lotions, emollients to be utilized in this study

3.3 Inclusion of Children and Minorities

Both male and female children of all races and ethnic groups are eligible for this trial.

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC*** and DF/PCC*** Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy within one month of registration. Issues that would cause treatment delays should be discussed with the Overall Principal

Investigator (PI). If a participant does not receive protocol therapy following registration within one month, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC*** Institutions

Applicable DF/HCC*** Policy REGIST-101 must be followed.

5. TREATMENT PLAN

This study aims to enroll 8 patients who will all receive in-person and written counseling for a daily preventative skin care regimen (PSCR) including instructions for daily safe sun protection, daily gentle skin care, nail care and every other day dilute bleach baths before the initiation of anti-cancer therapy. Patients will be recruited by the neuro-oncology team.

The preventative skin care regimen (PSCR) is detailed below. Patients will not have to purchase the following materials: sunscreen, gentle cleansers, moisturizers, emollients, bleach. These materials will be given to patients as the first study visit.

Safe sun protection will include instructions for:

- Use of SPF 30+ sunscreen with physical blockers (zinc oxide and/or titanium dioxide) whenever going outside
- Sunscreen to be reapplied every two hours (more often as needed)
- Sun-protective clothing including long sleeve, pants, wide-brimmed hat and sunglasses.

Gentle skin care will include:

- Daily short, lukewarm showers and water baths
- Gentle unscented cleansers (Dove, Cetaphil, Cerave, Vanicream) during bathing
- Thick and unscented moisturizing creams (Cerave cream, Vanicream, Cetaphil Cream, Dove), and emollients (Aquaphor, Vaseline) immediately following baths or showers every day.

Nail care will include:

- Trimming nails after bathing (fingernails once a week; toenails once a month)
- Keep the fingernails trimmed with a slight curve, but the toenail straight across, to prevent hangnails from forming.
- Do not pick loose bits off the nail to avoid tearing the nailbed or the cuticle.
- Cut them off neatly with a clean, sharp pair of scissors or a nail clipper.
- Avoid biting nails and trimming cuticles

Patients will also receive in-person and written counseling for every other day, 10-15 minutes dilute bleach baths.

Bleach baths will include:

- Mixing ¼ cup over-the-counter household bleach with ½ full tub of lukewarm water.
- Soak for 10-15 minutes
- Gently pat dry
- Apply gently moisturizers or emollients immediately following bathing
- In the case that patients do not have access to a tub and will make bleach bath compresses, or if a small infant tub is used, mix 1 teaspoon of bleach with 1 every 1 gallon of water

Patients will be asked to keep a diary of their daily skin care regimen and every-other-day dilute bleach baths including what products they used, how the bleach bath was made and how long they soaked in the bleach bath. This diary will be used to measure compliance.

If any patients develop a skin reaction to dilute bleach, they will discontinue and it will be documented.

If any patients develop a skin reaction to a moisturizer or sunscreen, we will recommend an alternative product, as we would do clinically.

Products mentioned above to be utilized in the preventative skin care regimen will be paid for by the Dermatology Research Fund at the Jimmy Fund Clinic***. External sites will supply their own sample products to participants.

5.2 Pre-Treatment Criteria

N/A

5.3 General Concomitant Medication and Supportive Care Guidelines

N/A

5.4 Criteria for Taking a Participant Off Protocol Therapy

Duration of intervention will be 12 weeks for each participant. They will receive skin examinations and interviews at the initiation of treatment, at 6 weeks (+/- 2 weeks) and at 12 weeks. Reasons for taking a participant off protocol intervention include the following

- Participant withdraws from targeted therapy
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with intervention protocols
- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Loss to follow-up
- Withdrawal of consent for data submission
- Death

Patients have the right to withdraw consent at any given time for any reason and no replacement is necessary as this is a single-arm trial. Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

The participant's status must be updated in OnCore in accordance with REGIST-OP-1.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Jennifer Huang at 617-355-1477***.

5.5 Duration of Follow Up

N/A

6. DOSING DELAYS/DOSE MODIFICATIONS

N/A

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1 Adverse Event List(s) for Commercial Agent(s)

Commercial agents for preventative skin care routines include gentle soaps, lotions, cleansers, moisturizers, and sunscreen. Adverse events from these agents may include skin irritation. Patients will be referred to product information included with purchase of these products for possible adverse events.

Commercial agents for dilute bleach bath include OTC bleach, with 1/4 cup to be placed into a ½ full bathtub. Adverse events from the this commercial agent may include eye irritation if contact with eyes and possible skin irritation. Patients will be

instructed to carefully avoid eye contact with bath water during dilute bleach baths and will be instructed to stop dilute bleach bath if skin irritation occurs following bleach baths.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Routine Adverse Event Reporting

All Adverse Events will be reported in Redcap.

7.3.1 DF/HCC*** Expedited Reporting Guidelines

Investigative sites within DF/HCC*** will report AEs directly to the DFCI Office*** for Human Research Studies (OHRS) per the DFCI*** IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC*** Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

N/A

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

N/A

9.1 Biomarker Studies

N/A

9.2 Laboratory Correlative Studies

N/A

9.3 Special Studies

N/A

10. STUDY CALENDAR

Section	Baseline	6 week (+/- 2 weeks) visit*	12 week visit	EDC Timepoints
PSCR counseling	X	X	X	Baseline, 6 week, 12 week
Informed consent	X	X	X	Baseline, 6 week, 12 week
Demographics	X			Baseline, 6 week, 12 week
Medical history	X	X	X	Baseline, 6 week, 12 week
MEK, BRAF, or Pan-RAF inhibitor dosing	X	X	X	Baseline, 6 week, 12 week
Skin exam and interview	X	X	X	Baseline, 6 week, 12 week
Severity Scores Completed	X	X	X	Baseline, 6 week, 12 week
Adverse events evaluation	X	X	X	Baseline, 6 week, 12 week

*6 week visit may be conducted virtually on request. Photographs will be requested prior to visit.

11. MEASUREMENT OF EFFECT

The measurement is the proportion (percentage) of patients with one or more cutaneous reaction to targeted BRAF, MEK or Pan-RAF inhibitor therapy. Secondary outcome measures include number of different cutaneous reactions experienced by each patient, severity of cutaneous reactions measured by the Common Terminology Criteria for Adverse Events (CTCAE), severity of xerosis measured by the Overall Dry Skin Score (ODS), severity of hand foot syndrome measured by the Hand-Foot Skin Reaction and Quality of Life Score (HFS-14), Pediatric Quality of Life Inventory General Well-Being Scale (PedsQL), and the Children's Dermatology Life Quality Index (CDLQI). To view these assessments and scoring in detail, please see Appendix A.

11.1 Antitumor Effect – Solid Tumors

N/A

11.1.1 Disease Parameters

Any new or changing skin, hair or nail findings

11.1.2 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. In the case of skin, hair or nail lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.1.3 Response Criteria

Severity of skin reactions will be graded according to the following severity scoring systems:

Common Terminology Criteria for Adverse Events (CTCAE) (Appendix A)
Overall Dry Skin Score (ODS) (Appendix B)
Hand-Foot Skin Reaction Quality of Life Score (HFS-14) (Appendix C)
Children's Dermatology Life Quality Index (CDLQI) (Appendix D)
Pediatric Quality of Life Inventory (PedsQL)

11.1.4 Response Review

Skin exams will be performed by dermatologists and trained research staff.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

Data will be reported in REDCap. The original plan was for each of the three sites to independently activate the protocol, and have their own separate, but identical, REDCap electronic case report forms (eCRFs). Each site has its own separate IRB approval for the trial. However, during study conduct, paper CRFs from the other two sites were sent to BCH, and the other sites' data were entered into the BCH REDCap eCRFs. All data for the trial currently reside at BCH; the existence of data at BCH is covered by two legal Data Sharing Agreements. All data is labeled by site. Keeping data transcribed as is will facilitate statistical analysis, and minimize further efforts towards data transfer.

13. STATISTICAL CONSIDERATIONS

Descriptive analysis of this cohort, including data from three sites, will be performed.

13.1 Study Design/Endpoints

The primary outcome measure is cutaneous reaction to targeted BRAF, MEK, or Pan-RAF inhibitor therapy. Secondary outcome measures include number of different cutaneous reactions experienced by each patient, severity of cutaneous reactions measured by the Common Terminology Criteria for Adverse Events (CTCAE), severity of xerosis measured by the Overall Dry Skin Score (ODS), severity of hand foot syndrome measured by the Hand-Foot Skin Reaction and Quality of Life Score (HFS-14), Pediatric Quality of Life Inventory (PedsQL), and the Children's Dermatology Life Quality Index (CDLQI).

13.2 Sample Size, Accrual Rate and Study Duration

Sample Size: 22 participants from three sites (DFCI [8], Toronto Sick Kids [7], Lurie Children's Hospital [7])
Accrual Rate: 6 participants / 1 year
Study duration: ~3 years (3 years of accrual + 12 weeks of treatment on the last patient enrolled)

This sample size is limited due to the rare nature of these cancers, but a total of 22 will be sufficient for descriptive analyses. The study team believes that accrual of more than 8 patients in a one year period at DFCI/BCH*** is not feasible.

13.3 Stratification Factors

N/A

13.4 Interim Monitoring Plan

N/A

13.5 Analysis of Primary Endpoints

In the overall cohort, the proportion of patients with one or more cutaneous reactions will be calculated, and a 95% exact confidence interval will be placed on this proportion.

13.6 Analysis of Secondary Endpoints

In the overall cohort, the minimum, maximum, and quartiles of the number of cutaneous reactions per patient will be calculated.

In the overall cohort: To describe the severity of cutaneous reactions, the proportion of patients at each CTCAE grade of toxicity, and for each grade of the Overall Dry Skin Score (ODS), will be calculated. For each of the following severity scales, the minimum, maximum, and quartiles of the scores will be calculated: Hand-Foot Skin Reaction and Quality of Life Score (HFS-14), Pediatric Quality of Life Inventory (PedsQL), and Children's Dermatology Life Quality Index (CDLQI).

13.7 Reporting and Exclusions

N/A

13.7.1 Evaluation of Toxicity

N/A

13.7.2 Evaluation of the Primary Efficacy Endpoint

N/A

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration.

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APPENDIX A SEVERITY SCORING SYSTEMS

1. Common Terminology Criteria For Adverse Events Version 5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location. **Navigational Note:** -					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body. **Navigational Note:** -					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid. **Navigational Note:** If infectious, consider Infections and infestations: Rash pustular or other site-specific Infections and infestations term.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture. **Navigational Note:** -					
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	-	-
Definition: A disorder characterized by skin which becomes itchy, red, inflamed, crusty, thick, scaly, and/or forms blisters. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Associated with electrolyte/hemodynamic imbalance	-	-
Definition: A disorder characterized by excessive sweating. **Navigational Note:** Synonym: Night sweats, diaphoresis					
Hyperkeratosis	Present	-	Limiting self-care ADLs	-	-
Definition: A disorder characterized by a thickening of the outer layer of the skin. **Navigational Note:** -					
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race. **Navigational Note:** -					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating. **Navigational Note:** -					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin. **Navigational Note:** -					
Nail changes	Present	-	-	-	-
Definition: A disorder characterized by a change in the nails. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center). **Navigational Note:** -					
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area. **Navigational Note:** -					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-
Definition: A disorder characterized by shrinking of adipose tissue. **Navigational Note:** -					
Hair color changes	Present	-	-	-	-
Definition: A disorder characterized by change in hair color or loss of normal pigmentation. **Navigational Note:** -					
Hair texture abnormal	Present	-	-	-	-
Definition: A disorder characterized by a change in the way the hair feels. **Navigational Note:** -					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen). **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nail discoloration	Asymptomatic; clinical or diagnostic observations only	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate. **Navigational Note:** -					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail. **Navigational Note:** -					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails. **Navigational Note:** -					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin. **Navigational Note:** -					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet. Also known as Hand-Foot Syndrome. **Navigational Note:** -					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation. **Navigational Note:** -					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color. **Navigational Note:** -					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back. **Navigational Note:** -					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin covering the top and the back of the head. **Navigational Note:** -					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis. **Navigational Note:** -					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition. **Navigational Note:** -					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment (e.g., vitiligo). **Navigational Note:** -					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin. **Navigational Note:** -					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the skin. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

2. Overall Dry Skin Score (ODS), EEMCO Guidelines

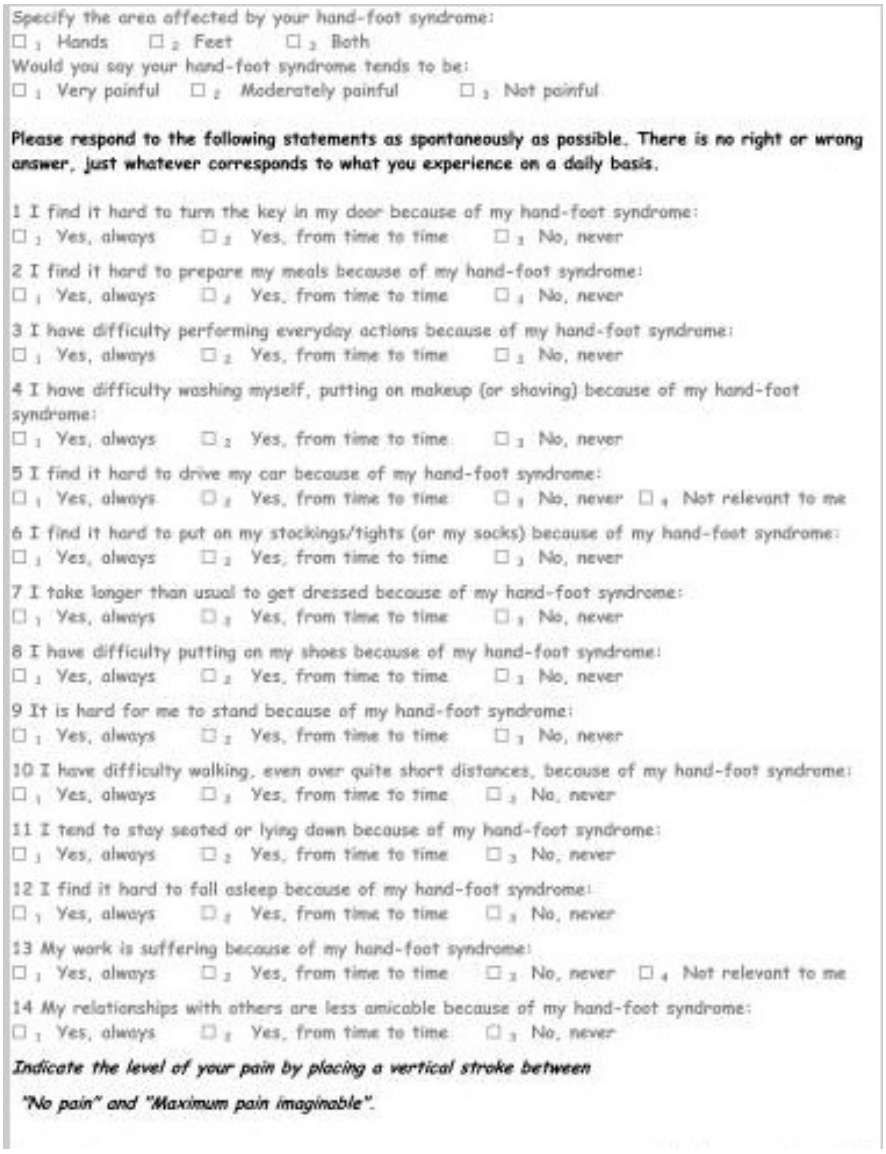
Kang BC, Kim YE, Kim YJ, Chang MJ, Choi HD, Li K, et al. Optimizing EEMCO guidance for the assessment of dry skin (xerosis) for pharmacies. *Skin Res Technol.* 2014;20(1):87-91.DOI: 10.1111/srt.12089

Score	Description
0	Absent
1	Faint scaling, faint roughness, and dull appearance
2	Small scales in combination with a few larger scales, slight roughness, whitish appearance
3	Small and larger scales uniformly distributed, definite roughness, possibly slight redness and possibly a few superficial cracks
4	Dominated by large scales, advanced roughness, redness present, eczematous redness and cracks

3. Hand-Foot Skin Reaction Quality of Life Score (HFS-14)

Sibaud V, Dalenc F, Chevreau C, Roche H, Delord JP, Mourey L, et al. HFS-14, a specific quality of life scale developed for patients suffering from hand-foot syndrome. *Oncologist.* 2011;16(10):1469-1478.DOI: 10.1634/theoncologist.2011-0033

Scoring:
Each item is scored on a three-point Likert scale: 0, "no, never"; 1, "yes, from time to time"; 2, "yes, always." Two separate questions include one to measure limb involvement (type of limb affected by HFS, one or both) and one to measure pain. The limb involvement item is scored either 1 if only the hands or feet were affected or 3 if both the hands and feet were affected. The pain item is scored on a three-point scale: 1, not painful; 2, moderately painful; 3, very painful. The total HFS-14 score is calculated by summing the scores of all items, with the higher the score, the greater the QoL impairment.



Specify the area affected by your hand-foot syndrome:
☐ 1 Hands ☐ 2 Feet ☐ 3 Both
Would you say your hand-foot syndrome tends to be:
☐ 1 Very painful ☐ 2 Moderately painful ☐ 3 Not painful

Please respond to the following statements as spontaneously as possible. There is no right or wrong answer, just whatever corresponds to what you experience on a daily basis.

1 I find it hard to turn the key in my door because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

2 I find it hard to prepare my meals because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

3 I have difficulty performing everyday actions because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

4 I have difficulty washing myself, putting on makeup (or shaving) because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

5 I find it hard to drive my car because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never ☐ 4 Not relevant to me

6 I find it hard to put on my stockings/tights (or my socks) because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

7 I take longer than usual to get dressed because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

8 I have difficulty putting on my shoes because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

9 It is hard for me to stand because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

10 I have difficulty walking, even over quite short distances, because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

11 I tend to stay seated or lying down because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

12 I find it hard to fall asleep because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

13 My work is suffering because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never ☐ 4 Not relevant to me

14 My relationships with others are less amicable because of my hand-foot syndrome:
☐ 1 Yes, always ☐ 2 Yes, from time to time ☐ 3 No, never

Indicate the level of your pain by placing a vertical stroke between "No pain" and "Maximum pain imaginable".

4. Children's Dermatology Life Quality Index (CDLQI)
(Illustrations not included)

Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol.* 1995;132(6):942-949

https://astar-register.org/wp-content/uploads/sites/284/2018/10/CDLQI-Cartoon English-V1-16Oct18.pdf

How to score it

The scoring of each question is:

- Very much = 3
- Quite a lot = 2
- Only a little = 1
- Not at all = 0
- Question unanswered = 0
- Question 7: 'Prevented school' (text-only questionnaire) = 3
-
- Meaning of scores

- 0-1 = no effect on child's life
- 2-6 = small effect
- 7-12 = moderate effect
- 13-18 = very large effect
- 19-30 = extremely large effect

Please Check EVERY question.

Over the last week:

1. How itch, '**scratchy,' sore** or **painful** has your skin been?
Very much
Quite a Lot
A Little
Not at all

2. How **upset** or **embarrassed, self-conscious,** or **sad** have you been because of your skin?
Very much
Quite a Lot
A Little
Not at all

3. How much has your skin affected your **friendships?**
Very much
Quite a Lot
A Little
Not at all

4. How much have you changed or worn **different** or **special clothes/shoes** because of your skin?
Very much
Quite a Lot
A Little
Not at all

5. How much has your skin trouble affected **going out, playing** or **doing hobbies?**
Very much
Quite a Lot
A Little
Not at all

6. How much have you avoided **swimming** or **other sports** because of your skin trouble?
Very much
Quite a Lot
A Little
Not at all
7a. If **school time:** How much did your skin trouble affect your **school work?**
Very much
Quite a Lot
A Little
Not at all

7b. If **holiday time:** How much has your skin problem interfered with your **holiday plans?**
Very much
Quite a Lot
A Little
Not at all

8. How much trouble have you had with your skin with other people **calling your names, teasing, bullying, asking questions,** or **avoiding you?**
Very much
Quite a Lot
A Little
Not at all

9. How much has your **sleep** been affected by your skin problem?
Very much
Quite a Lot

A Little
Not at all

10. How much of a problem has the **treatment** for your skin been?
Very much
Quite a Lot
A Little
Not at all

5. Pediatric Quality of Life Score, General Well-Being Scale
https://www.pedsql.org/

For scaling and scoring:
https://www.pedsql.org/PedsQL-Scoring.pdf