BMT CTN Protocol #0801

PROVIDER SURVEY MANUAL
FOR
COMPREHENSIVE CHRONIC GVHD ASSESSMENT

A Phase II/III Randomized, Multicenter Trial Comparing Sirolimus plus Prednisone, Sirolimus/Extracorporeal Photopheresis plus Prednisone, and Sirolimus/Calcineurin Inhibitor plus Prednisone for the Treatment of Chronic Graft-versus-Host Disease

Version 1.0
**Guiding Principles:**

*Key Point –
History refers to *within* the last 7 days*

- **SKIN**
  - Q1: Do you have severe skin itching (pruritus)? (S1: Item 10)
    - YES □ NO □

- **ORAL**
  - Q2: Is your mouth dry?
    - YES □ NO □
  - Q3: Any sensitivity to food, hot, cold, spice, toothpaste, soda?
    - YES □ NO □
  - Q4: Any mouth sores or ulcers?
    - YES □ NO □
  - Q5: Do mouth symptoms limit your eating?
    - NO □ PARTIALLY □ IN A MAJOR WAY □
  - Q6: Do you take narcotic medications to relieve your mouth symptoms? (S2; Item 5, 10)
    - YES □ NO □

- **GASTROINTESTINAL**
  - Q7: Do you have any of the following:
    - □ nausea
    - □ vomiting
    - □ diarrhea (S3: Item 1)
    - □ abdominal pain?
  - *If no diarrhea skip to Q10*
  - Q8: Did loose or liquid stools occur during the past week on: (S3:Item 4)
    - □ some days,
    - □ every day or,
    - □ almost every day
  - Q9: Did you receive I.V. or extrafluids during the past week to prevent or treat fluid loss from diarrhea? (S3: Item 4)
    - YES □ NO □
  - Q10: How is your appetite? (S3: Item 1)
    - □ Poor or reduced from normal
    - □ Normal
    - □ Increased
  - Q11: Are you easily full when eating? (S3:Item 1)
    - YES □ NO □

- **If no anorexia, early satiety, nausea or vomiting then skip to Q14**
  - Q12: Did your lack of appetite, early fullness when eating, nausea, or vomiting cause you to eat less during the past week?
    - YES □ NO □
  - Q13: Was your lack of appetite, early fullness when eating, nausea, or vomiting: (S3: Item3)
    - □ Occasional throughout the week,
    - □ Intermittent throughout the day
    - □ Persistent throughout the day
  - Q14: How much do you normally weigh?
    - _______ Lbs / kg.
  - Q15: Have you had any weight loss?
    - YES □ NO □ (S3: Item 1)

- **If no weight loss skip to Q17**
  - Q16: How much weight loss?____Lbs (or) kg divided by answer to Q14 x 100 = ____% loss
  - Q17: Is it painful to swallow?
    - YES □ NO □
  - Q18: Do food or pills get stuck?
    - YES □ NO □
  - Q19: Can you easily swallow liquid or soft foods?
    - YES □ NO □

- **If no swallowing problems skip to Q21**
  - Q20: Did you have swallowing difficulties for almost everything on almost every day of the week this past 7 days? (S3: Item 2)
    - YES □ NO □

- **OCULAR**
  - Q21: Are your eyes dry or excessively teary?
    - YES □ NO □ (S4: Item 1)
  - Q22: Do you use artificial tears? (S4: Item 1)
    - YES □ NO □ If yes: □ ≤3 x, or □ > 3x per day
  - Q23: Have you had your tear ducts plugged or cauterized? (S4: Item 1)
    - YES □ NO □
  - Q24: Does your eye dryness affect your vision or prevent you from working? (S4: Item 1)
    - YES □ NO □
  - Q25: Do you wear special eyewear or scleral lenses to relieve pain? (S4: Item 1)
    - YES □ NO □

- **JOINTS / FASCIA**
  - Q26: Are your arms, legs or joints tight?
    - YES □ NO □ (S1: Item 11, S4: Item 2)

*If yes, ask:*
  - Q27: How does the tightness affect your ADLs? (S4: Item 2)
    - □ NOT AT ALL □ MODERATELY
    - □ SEVERELY (unable to dress self, etc)

- **GENITAL**
  - Q28: Any vaginal (or penile,foreskin) dryness and/or discomfort during sexual intercourse or during a GYN exam? (S4: Item 3)
    - YES □ NO □

*If yes: □ MILD □ MODERATE □ SEVERE*
LUNG

Q29: Do you get short of breath? (S4: Item 5)
Yes □ No □
If yes, ask:
Q30: When do you get short of breath:
□ ONE FLIGHT OF STAIRS
□ WALKING ON FLAT GROUND
□ AT REST (may need oxygen)

You now have 12% of the data to complete the 0801 provider survey!

Step 2 – Streamlined Physical Exam:

Begin with the gowned patient sitting on exam table towards you

A) Evaluate range of motion:
   a. Buddha Prayer position
   b. Straighten elbows
   c. Raise upper arms next to ears
   d. Dorsiflex ankles

Complete Section 2: Items 1-4

Q1: What is best ROM at Shoulder?
Q2: What is best ROM at Elbows?
Q3: What is best ROM at Wrists/Fingers?
Q4: What is best ROM at Ankle Dorsiflexion?

Now put on gloves for the exploration of all five oral surfaces and grab a halogen light

B) Evaluate ORAL cavity in 60 secs:
   Take four separate 5 second looks to create a minds-eye view that focuses sequentially on each of erythema, lichenoid lesions, ulcers and mucoceles.

*Key Point –
TOTAL MOUTH AREA for the oral exam comprises five oral surfaces: ~20% right buccal, ~20% left buccal, ~20% lips and labial, ~20% dorsal tongue, ~20% lateral tongue and soft palate (don’t count hard palate).

   a. Erythema
      Simply “eyeball it” to categorize your 5 second visual snapshot as follows:

Complete Section 2: Item 6

Q5: Is severe erythema present on > 1 of the five surfaces (this almost guarantees that at least 25% of the total oral surface is severe)?
   Yes □ No □ If yes: Score “3” = Severe
Q6: Is mild erythema present on any % of oral surfaces without any severe areas and less than a quarter of the total oral surface being moderately red?
   Yes □ No □ If yes: Score “1” = Mild
Q7: Is there any erythema that is neither mild nor severe (ie. anything in between)?
   Yes □ No □ If yes: Score “2” = Moderate

Figure 1 – Erythema: clockwise from top left: moderate 25% and severe <25% (arrowed), mild and moderate < 25%, severe > 25%, moderate and severe with severe > 25% (ulcer also shown by arrow).

   b. Lichenoid lesions
      Next eyeball all oral surface (white)
      lichenoid change to categorize as:

Complete Section 2: Item 7

Q8: Do lacy or confluent white lesions cover:
   i) □ less than a quarter? (Score “1”, Mild)
   ii) □ more than a half? (Score “3”, Severe)
   iii) □ between (i) & (ii)? (Score “2”, Moderate)

Figure 2 – Lichenoid changes: clockwise from top left: lichenoid changes on lower lip and dorsal tongue, buccal mucosa, lateral tongue and, emanating from labial mucosa to lip.
c. Ulcers

Ulcers are a 5 second snap decision:

Complete Section 2: Item 8
Q9: Do ulcers cover any area that is:
i) □ more than one of the five component oral surfaces? (Score “3”, Severe)
ii) □ less than one of the five component oral surfaces? (Score “2”, Moderate).

Figure 3 – Ulcers: covered with yellowish pseudomembranous exudate.

d. Mucoceles

Glimpse the everted lower lip and soft palate for number of mucoceles:

Complete Section 2: Item 9
Q10: Is the mucocele count:
i) □ more than 10? (Score “3”)
ii) □ less than 5? (Score “1”).
iii) □ in between (i) & (ii)? (Score “2”).

Figure 4 – Mucoceles: More than 10 present on the soft palate in isolation or in clumps (arrowed).

C) Evaluate SKIN in 8-10 minutes:

The goal is to quantify the extent of erythema, dyspigmentation, moveable and non-moveable sclerosis by first using the Vienna Skin Score and second, extrapolating this data to complete the NIH Skin Scores.

*Key Points –
a) NIH “Erythematous rash” includes maculopapular lesions and erythroderma but also rashes that are not always red (lichen-planus like, papulosquamous, poikiloderma, keratosis pilaris-like).
b) Moveable sclerosis is usually superficial but sclerosis of deeper abdominal tissue can also be moveable when it does not extend to involve also the epidermis.
c) NIH uses rule of 9’s + 1% for genitals
d) The Vienna Skin Scale (VSS) splits the NIH area “2” (Anterior Torso) into: “9” (Chest) and “10” (Abdomen).
e) VSS includes “Genitals” in area “10” as part of the Abdomen but NIH keeps “Genitals” separate in area “8”.
f) VSS splits the NIH area “5” (Upper Extremity) into: “1” (Hand) and “3” (Arm)
g) NIH incorporates buttocks into the areas “6” and “7” (Lower extremities) but VSS incorporates buttocks into area “6” (back).
h) NIH & VSS are congruent for head/neck

Remove gloves. With the patient still sitting on exam table towards you begin skin exam

LOOK for:
(i) Classic lesions (lichenplanus, lichen-sclerosis, morphea, sclerosis, poikiloderma), see glossary.
(ii) Distinct lesions (dyspigmentation, nail and hair changes, papulosquamous lesions), see glossary.
(iii) Extent of erythema, see glossary.
FEEL skin:
(i) Is it normal? (VSS = 0)
(ii) Is it thickened? (VSS = 2-4)

MOVE skin that is thickened:
(i) Is it fully moveable (VSS = 2)
(ii) Is it poorly moveable but pinchable (VSS = 3)
(iii) Is it hidebound (not pinchable VSS = 4)

*Key Points:
 a) It is most efficient to continue examining each body area using an iterative “LOOK, FEEL, MOVE” approach in the order listed below stopping as indicated to complete the form where indicated
 b) Don’t forget to check “Yes” for ONE sentinel lesion and “No” for ALL non-sentinel areas.
 c) Don’t forget to score the fraction of mobile or hidebound skin that is ALSO red.

| a. Left hand (S1: Item 32) |
| b. Right hand (S1: Item 30) |
| c. Left arm (S1: Item 31) |
| d. Right arm (S1: Item 29) |
| e. Head and neck (S1: Item 25) |

**Ask the patient to lie prone and expose back/buttocks but cover legs**

| f. Back and Buttocks (S1: Item 28) |

**Ask the patient to roll over and lie supine to expose the front of the legs (cover the chest and abdomen) and continue “g” and “h”**

| g. Right leg and foot (S1: Item 33) |
| h. Left leg and foot (S1: Item 34) |

**Ask the patient to lie prone and expose back/buttocks but cover legs**

| i. Chest (S1: Item 26) |
| j. Abdomen (S1: Item 27) |
| k. Genitals (In VSS is combined with abdomen) |

Using the data collected so far you should now be able easily to complete Section 1: Items 1-24

Q11: Complete NIH scoring for 8 body areas.
Q12: Check any diagnostic or distinctive skin changes: (S1: Items 9, 17, 19)
□Poikiloderma?
□Lichen planus-like lesions

- Sclerotic-features
- Morphea-like features
- Depigmentation (vitiligo-like)

Q13: Check all other skin changes: (S1: Items 12-16, 18, 20-24)
□Macular or maculopapular rash?
□Pruritus of any severity
□Keratosis pilaris
□Papulosquamous lesions or ichthyosis
□Hair: thinning, premature graying, coarse or dull scalp hair, patchy hair, alopecia
□Nails: longitudinal ridging, splitting, onycholysis, pterygium unguis, or nail loss

Q14: Any Ulcers? (S1: Items 12-14)
YES □ NO □ If yes: Largest dimension __ cm, Location: ____________________________

If no sclerosis skip to Q15
Q15: Is there skin thickening that is:
□ Moveable? (S1: Item 9)
□ Moves poorly or is hidebound or ulcerated?

You now have 52% of the data to complete the 0801 provider survey!

Step 3 – Remaining Provider Items:

Complete Section 5: Parts 1-4 (22 Items)
Overall Status is self explanatory and takes less than minutes.

Complete Section 6: Items 1-17
Checklist of other indicators, manifestations or severe complications of chronic GVHD.
(Takes 1 minute)

You now have 91% of the data to complete the 0801 provider survey!

Step 4 – Delegatable Lab/test Items

(not in the Provider Survey but part of NIH assessment):

**A) SCHIRMER’S TEST PROCEDURE:**

1) Wash hands and put on non-sterile gloves.
2) Fold Schirmer strips
3) Ask patient to look up, gently displace the lower lid down, and place Schirmer strip on the inferior fornix laterally with the fold at palpebral margin. Allow filter strip to drape below eye.
4) When placing Schirmer strip in second eye, instruct patient to use his/her finger to gently hold the contralateral eye closed.
5) Schirmer strip remains in place for 5 mins
6) Remove strip and compare wetting to interpretation grid, recording the number of millimeters of wetting for each eye.

*Key Point:
Do not use topical anesthetic for the test
B) GRIP STRENGTH PROCEDURE:

1) Patient sits in chair, arms unsupported.
2) Shoulder is adducted and in neutral position.
3) Elbow at 90 degrees, forearm neutral, wrist at 0-30 degrees of extension.
4) Instruct patient to squeeze dynamometer with as much force as possible, using the dominant hand.
5) Repeat for a total of 3 times and record results of each attempt.

*Key Points:
   a) Illustrate use of the dynamometer to the patient prior to testing.
   b) Pause for 10-20 seconds between each of the 3 attempts to avoid muscle fatigue
   c) Record results consistently in “psi” (pounds per square inch)

C) TWO MINUTE WALK PROCEDURE:

1) Establish a lap course of 50 feet in length in a clinic or office hallway.
2) Mark the start and finish points of the lap with marker rings.
3) Set the lap counter and stopwatch to zero.
4) Explain to the patient: “The object of this test is to walk as far as possible in 2 mins. You will be walking back and forth between the marker rings. You should pivot briskly at the marker ring and continue back without hesitation. Now I am going to show you.”
5) Demonstrate by walking one lap yourself and pivot briskly at the marker ring.
6) Continue with: “Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at the ring marker. Remember that the object is to walk as far as possible for two minutes, but don’t run or jog. Are you ready to start?”
7) As soon as the patient starts to walk, start the stopwatch.
8) Each time the patient turns at the marker to begin a new lap, click the lap counter once.
9) When the stopwatch shows that 1-minute has elapsed, tell the patient “You are doing well, you have one minute to go.”
10) When the stopwatch shows 1-min and 45 secs say: “In a moment, I am going to tell you to stop. When I do, just stop right where you are, and I will come to you.”
11) When the full 2 mins have elapsed, say “Stop”. Walk over to the patient and mark the spot where he/she stopped by placing the ring marker on the floor.
12) Measure in feet the distance covered in the final partial lap. Record this distance along with the number of laps, and calculate the total distance traveled in 2 minutes.

*Key Points:
   a) The lap course should be straight, without obstacles or traffic, and well lit.
   b) The patient should be wearing appropriate walking shoes.
   c) The patient should feel well (no dizziness, light headedness, chest pain or dyspnea).
   d) Do not talk to anyone during the walk. Watch the patient and do not allow yourself to be distracted and lose count of the laps. Each time the patient turns at the marker to begin another lap.

Now record the remaining test items:

Q1: What is the mean of the Schirmer’s tear test for both eyes? _____mm

Q2:
   a) How many laps were done in the 2-minute walk? _______ laps
   b) How many feet were covered in the final partial lap? _______ feet
   c) Total distance in 2 minutes = [Answer to (a) x 50] + [Answer to (b)] _______ feet

Q3: What is the grip strength in the dominant hand?
   1st attempt: _______ (p.s.i.)
   2nd attempt: _______ (p.s.i.)
   3rd attempt: _______ (p.s.i.)

Q4: What is the platelet count? _______ /μL
Q5: What is the serum bilirubin? _______ mg/dL
Q6: What is the serum ALT? _______ U/L
Q7: What is the serum Alk. Phos? _______ U/L

Q8: What is the FEV1? _______% predicted
Q9: What is the DLCO? _______% predicted

You now have 100% of the Data to complete the Comprehensive 0801 chronic GVHD Assessment!!
Glossary of Skin Lesions

ERYTHEMA
(Can be a sign of BOTH acute and chronic GVHD)

Fine mobilliform erythematous rash

Erythroderma

LICHEN PLANUS
(Classic Diagnostic sign of chronic GVHD)

Papular erythematous rash

Lichen planus-like

Erythroderma

Lichen planus-like
**LICHEN SCLEROSUS-LIKE**
(Classic diagnostic sign of chronic GVHD)

- Lesions tend to be grouped in discrete patches and show “cigarette paper” wrinkling

**MORPHEA**
(Classic diagnostic sign of chronic GVHD)

- Lesions tend to be have central fibrotic hypopigmented area and a slightly hyperpigmented border

**POIKILODERMA**
(Classic diagnostic sign of chronic GVHD)

**SCLEROSIS**
(Classic diagnostic sign of chronic GVHD)

- Lesional tissue is hard and fibrous, thickened and when superficial is usually movable upon palpation, but becomes less movable, and then only pinchable as it progresses towards becoming hidebound, fixed and non-moveable.
Deep Sclerosis/Fasciitis ("Groove Sign")

Deep Sclerosis (Rippling, Dimpling, "cellulite" appearance)

Hidebound Sclerosis with erythema and Ulcers

Deep Sclerosis/Fasciitis ("Groove sign" black arrow, "Dimpling sign" white arrow, fixed elbow contractures, papulosquamous plaque shown by green arrow)

PAPULOSQUAMOUS LESIONS (Distinctive but non-diagnostic sign of chronic GVHD)

Papulosquamous lesions
Components of the NIH CGVHD Assessment Diagnosis Response

Core Measures
1. Clinician assessed signs and symptoms
2. Patient assessed signs and symptoms
3. CGVHD Symptom Scale (Lee)
4. Clinician reported global ratings (4pt, 7pt or 11pt)
5. Patient reported global ratings

Ancillary Measures (optional)
1. Grip strength
2. 2 minute walk time
3. HAP questionnaire (patient reported measure of activity)
4. KPS (clinician assessed)
5. SF36 v2.0 (QoL, patient)
6. FACTBMT (QoL, patient)
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