BMT CTN Technical Document

Acute & Chronic GVHD Guidance

1. Acute Graft-Vs-Host Disease (GVHD)

1.1. Introduction

The Acute GVHD Technical Committee has reviewed and recommends the following procedures for acute GVHD evaluation, data collection, scoring, and final acute GVHD severity evaluation for clinical trials performed through the Network.

1.2. Mission Statement

The purpose of the Acute GVHD Technical Committee is to define data collection, grading schemes, and study requirements for pathologic confirmation.

1.3. Acute GVHD Staging and Grading

1.3.1. Records

Investigators should document on a weekly basis (beginning with the day of transplant) the raw data for the GVHD target organs either in the medical record directly or on a trial-specific worksheet. This documentation should include the extent of skin rash, if any; the total bilirubin; the daily diarrhea output; or number of diarrhea episodes per day if volumes are not available (each episode of diarrhea to be estimated at a volume of 200 mL), and the presence or absence of upper GI symptoms (severe nausea (≥3 days), vomiting ≥2 episodes/d for ≥2 days), and/or anorexia with weight loss). Staging is performed according to the MAGIC guidance (Harris, et al, BBMT, 2016). GVHD staging on the date of diagnosis and the date of systemic treatment should be recorded (these can be the same day) and subsequent weekly staging should be the staging closest to the 7- day interval from the start of treatment (or diagnosis if not systemically treated). Biopsy confirmation of target organs is recommended in most circumstances to confirm the diagnosis of acute GVHD.

In addition to the raw data record to verify acute GVHD organs staging, the relevant differential diagnoses should be recorded (e.g., drug rash, GI infection such as C. difficile, veno-occlusive disease (VOD), total parenteral nutrition (TPN), etc.) each week for target organ involvement. The record should indicate whether a biopsy was performed, and if the biopsy results confirmed or were consistent with a diagnosis of GVHD (GVHD is clearly identified as present on the biopsy, with or without other coexisting processes present on the biopsy), confirmed or consistent with a non-GVHD diagnosis (unequivocal evidence of a diagnosis other than GVHD without concomitant features suggestive of GVHD), were inconclusive (no abnormalities identified, or subtle changes noted that are insufficient to identify an etiology, or insufficient tissue for interpretation) or equivocal (findings are present consistent with GVHD and other etiologies, but the pathologist cannot definitively confirm the presence of GVHD), for each organ involved. Because GVHD is a clinical diagnosis, confirmed, consistent, and equivocal results can be used to support a diagnosis of GVHD in the appropriate clinical context.

1.3.2. Conclusions

Each center's conclusion about GVHD involved in the organ (yes/no), stage, and biopsy information should be collected and used by grading algorithms to determine maximum overall grade.

1.3.3. Staging and Grading

Acute GVHD staging and grading should be performed by the MAGIC criteria (Harris, et al, BBMT, 2016) which are based on the Przepiorka criteria (Przepiorka, et al, 1995) with additional and detailed guidance. Key differences between Przepiorka criteria and MAGIC criteria include upgrading stage 4 GI GVHD to grade IV, including bloody diarrhea in staging, an option to stage lower GI GVHD on number of episodes of diarrhea, establishing severity and duration criteria for upper GI symptoms in the absence of a biopsy, and clarifying skin GVHD is staged on active rash only. See GVHD Clinical Staging table below.

GVHD CLINICAL STAGING

GVHD clinical staging will be according to the MAGIC criteria below

	Stage 0	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
Skin	No rash	Maculopapular rash < 25% BSA	Maculopapular rash 25-50%	Maculopapular rash > 50%	Generalized erythroderma (>50% BSA) **plus** bullae and/or desquamation >5% BSA
Liver	Bilirubin < 2 mg/dl	2-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl
GI tract	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day	Severe abdominal pain +/- ileus, frank blood or grossly bloody stool (regardless of stool volume)
UGI		Severe/persistent nausea/vomiting/ anorexia			

- For GI GVHD, child is defined as <18 years of age and <50 kg weight
- Upper GI GVHD: in the absence of a biopsy, symptom severity and duration require nausea ≥3 days, and/or ≥ 2 vomiting episodes per day for at least two days, and/or anorexia with weight loss
- For stage 4 GI GVHD, severe abdominal pain is defined as (1) pain that requires opioid use **and** (2) pain that significantly impacts on performance status as determined by the treating physician

Overall Clinical Grade:

Grade 0	No stage 1-4 of any organ
Grade I	Stage 1-2 skin and no liver or GI involvement
Grade II	Stage 3 skin and/or Stage 1 liver and/or Stage 1 GI
Grade III	Stage 0-3 skin with Stage 2-3 liver and/or Stage 2-3 GI
Grade IV	Stage 4 in any target organ (skin, liver, GI)

1.4. Data Collection

Weekly GVHD raw data, staging, and grading should be collected until 60-70 days post-transplant for all patients and to Day +100 if feasible. Subsequently, monthly data involving acute GVHD symptomatology should be collected for all patients remaining on immunosuppressive therapy until two months after discontinuation of immunosuppressive treatment for acute GVHD. If acute GVHD develops later or flares, the data collection should be continued frequently (every 1, 2, or 4 weeks as feasible) in sufficient detail to monitor the progress of the disease. The definition of a GVHD flare is not yet standardized but recent BMT CTN studies have defined a GVHD flare as any progression of acute GVHD after an initial response (ie, earlier CR or PR) that requires re-escalation of steroid dosing (at least 10 mg/d prednisone or equivalent; or as specified by protocol), or initiation of additional systemic therapy.

1.5. Other Staging Schema

Sufficient clinical information is not available or published to distinguish any differences in acute GVHD patterns following non-myeloablative transplants, cord blood transplants, or after DLI. In these settings, acute GVHD organ involvement staging, and grading should follow the same plan described above, unless subsequent re-evaluation documents the need for alternative staging and grading schema.

1.6. Acute and Chronic GVHD syndromes

Historically, any GVHD developing after Day +100 post-HCT was called chronic GVHD. However, signs and symptoms of acute GVHD can occur beyond Day +100, especially in patients who received reduced-intensity conditioning regimens or DLI. According to the National Institutes of Health (NIH) Criteria for diagnosis and staging of chronic GVHD (see below), it is clinical manifestations and not timeframe after transplantation that determine whether GVHD is acute or chronic (See Table A). Further, acute GVHD includes *classic acute GVHD* (occurring $\leq$ Day +100) and *late acute GVHD* (occurring > Day +100), both in the absence of chronic GVHD. Chronic GVHD syndrome includes *classic chronic GVHD* (manifestations that can be attributed only to chronic GVHD) and *overlap syndrome* (features of both acute and chronic GVHD), discussed below.

2. CHRONIC GRAFT-VS-HOST DISEASE (GVHD)

2.1. Introduction

The Chronic GVHD Technical Committee has reviewed and recommended the following procedures for chronic GVHD diagnosis and staging, evaluation, data collection, and treatment response assessment for clinical trials performed through the Network.

The NIH Consensus Conferences have provided standardized measures for diagnosis, staging, and assessing response to therapy of chronic GVHD. The NIH Criteria for diagnosis and staging are accepted as the Standard of Care for both clinical practice and clinical trials design (Jagasia, et al, BBMT 2015). In addition, the NIH has developed a standard tool to measure therapeutic response for chronic GVHD in clinical trials (Lee, BBMT 2015). **Thus, diagnosis and staging criteria are intended for baseline and cross-sectional use in clinical practice whereas response criteria are intended for longitudinal evaluation in clinical trials.** The use of standardized assessment methods will enhance uniformity and feasibility of data collection and allow comparison of efficacy between different agents in clinical trials.

2.2. Mission Statement

The Chronic GVHD Technical Committee will revise this chapter periodically, as new knowledge is gained, and therapeutic practices evolve. For each individual BMT CTN protocol, more or less information regarding chronic GVHD may be required. The Chronic GVHD Technical Committee will provide advice to the Principal Investigator (PI) of each protocol as to the frequency and detail with which chronic GVHD severity should be assessed.

2.3. Diagnosis and Clinical Manifestations of Chronic GVHD

Chronic GVHD can target the skin, eyes, mouth, gastrointestinal tract, liver, lungs, joints, muscle, fasciae, genital tract; it may be restricted to a single site, but frequently several organ systems are involved. The diagnosis of chronic GVHD requires at least one *diagnostic sign* (manifestation that establishes the diagnosis of chronic GvHD without the need for further testing) or at least one *distinctive sign* (manifestation highly suggestive of chronic GvHD but insufficient alone to establish the diagnosis) confirmed by biopsy, laboratory test, eye examination or by radiology in the same or another organ (i.e., ophthalmologist examination findings). In addition, it is important to make a distinction from acute GVHD and exclude other possible etiologies. Common features are found in both acute and chronic GvHD and cannot be used to distinguish between the two disorders (see Table B). Biopsy or other testing is always encouraged but is not mandatory if the patient has at least one diagnostic sign/symptom.

The term "*overlap*" refers to the presence of at least one acute GVHD manifestation in a patient with diagnosis of chronic GVHD. In the absence of features fulfilling criteria for the diagnosis of chronic GVHD, the persistence, recurrence, or new onset of characteristic skin, gastrointestinal tract or liver abnormalities should be classified as acute GVHD regardless of the time after transplantation.

2.4. Organ Scoring and Global Scoring of Chronic GVHD

The scoring system can be applied only after the diagnosis of chronic GVHD has been established. Eight organs are assessed: skin, eyes, mouth, GI tract, liver, lungs, joints and fascia, and genital tract. Each organ is scored according to a 4-point scale (0–3) with 0 representing no involvement and 3 reflecting severe impairment (see Table D). The NIH global severity for chronic GVHD (mild, moderate, severe) is then derived by combining organ-specific scores (see Table C).

Organ scoring also incorporates the attribution of abnormalities not due to chronic GVHD. Sites or organs with abnormality unequivocal documentation of attribution to other causes than GVHD should NOT be evaluated and are not included in computing the overall severity, but the data are collected in the scoring form and the box "*Abnormality present but explained entirely by non- GVHD documented cause*" should be checked so the organ can be excluded from global score calculation. If there are multifactorial etiologies to explain abnormalities including chronic GVHD, the abnormality is scored as if the entire deficit is due to GVHD.

2.5. Data Collection

The proposed NIH measurement criteria to evaluate response in chronic GVHD is necessary for longitudinal evaluation in therapeutical clinical trials. The extent to which chronic GVHD manifestation will be monitored and what data will be collected, might vary from trial to trial and will be stated in advance by the PI of the protocol. For some studies, medical photographs may be useful to record severity and response to treatment. Case report forms are available in AdvantageEDC, Advantage eClinical or other electronic data capture system. Appropriate documentation of the assessment and data collection should be performed in real time, whenever possible.

2.6. Proposed Measures for Clinical Trials Response Assessment

"Chronic GVHD-specific" core measures are:

(a) Assessment of Chronic GVHD Activity by the Clinician (see Table D) and by the Patient-self Report (see Table E),

(b) The Lee Chronic GVHD Symptom Scale (see Table F), and

(c) The clinician-assessed or patient-reported *global rating scales* (see Table G; the MD Anderson Symptom Inventory (Cleeland Cancer 2000) and the 7-point change scale (Osaba JCO 1998)).

Physicians, nurse practitioners, or physician assistants should provide a subjective assessment of current overall chronic GVHD severity on a 4-point scale (no chronic GVHD, mild, moderate, severe) (Lee, Cook, Soiffer, BBMT 2002) without knowledge of the calculated NIH global severity score (see Table C). They should also provide an assessment of current overall chronic GVHD severity on an 0-10-point numerical scale (0 indicates no GVHD manifestations; 10 indicates most severe chronic GVHD symptoms possible) (Preston, Colman, Acta Psychol (Amst) 2000). The categories of mild, moderate, and severe have been used in previous studies for patient and clinician assessment, where they were often undefined but showed good prognostic ability (Lee, BBMT 2002, Lee, Blood 2002). Similarly, clinicians should also provide their evaluations of chronic GVHD changes since the last assessment scored on a 7-point scale (very much better, moderately better, a little better, about the same, a little worse, moderately worse, very much worse) (Osoba, D, J Clin Oncol 1998). All of these assessments are included in the Clinician Assessment Form (see Table D).

"Chronic GVHD non-specific" ancillary measures for adults include either the Medical Outcomes Study Short Form 36-item questionnaire **(**SF-36) or the Functional Assessment of Cancer Therapy–Bone Marrow Transplantation subscale (FACT-BMT) plus the Human Activity Profile (HAP) questionnaire. These measures are strongly encouraged but remain optional and should not be used as primary endpoints in chronic GVHD trials.

Age-appropriate modifications of existing measures should be used in children with chronic GVHD, see below.

Measurements should be made at regular intervals, for example every three months, and whenever a new systemic immunosuppressive treatment is started, or the patient stops study treatment. Documenting response involves a comparison of chronic GVHD activity at 2 time points. The proposed consensus definitions of response are offered for each organ and for overall outcomes (see Table H), although each protocol should define precisely how response will be determined. Efforts to document the durability of response are strongly encouraged. Three general categories of overall response are proposed for interpretation of clinical trials: CR, PR, and lack of response (stable disease, mixed response, progression). *CR* is defined as resolution of all manifestations in each organ or site, and *PR* is defined as improvement in at least 1 organ or site without progression in any other organ or site as described in the following sections on organ response. Mixed response is a new category defined as CR or PR in at least 1 organ accompanied by progression in another organ.

Measures that predict outcomes but are not sensitive to change or do not directly measure chronic GVHD manifestations should be collected at baseline but not used in the response assessment, for example: performance status, platelet count, eosinophils, and the two-minute walk test.

2.7. Additional Caveats for Chronic GVHD Assessment

- Protocols must specify the times when response will be assessed and the requirements for durability of response.
- The protocol should specify whether dose changes, for example increased steroid doses, are considered "additional systemic therapy."
- Specific reasons for additional systemic therapy should be collected, as new treatments are sometimes added even though chronic GVHD is stable or improving (e.g., loss or change of insurance coverage, transportation or logistical issues, loss of central iv access etc.), and protocols should specify whether these cases should be categorized as lack of response.
- Protocols should specify whether topical or organ-directed therapies are allowed during the course of the trial or would automatically indicate a lack of response or would designate the patient as "not evaluable." Topical and local therapy added after study enrollment must be documented in all patients.
- PIs of specific BMT CTN protocols should estimate what, if any, variations in medical management of chronic GVHD might potentially confound their primary or secondary outcomes. If there are serious concerns that practice variation might confound interpretation of endpoints, the Chronic GVHD Technical Committee will assist the PI in determining what data will be necessary to monitor such practices or will provide recommendations for standardization of those practices such that they may be collected prospectively.
- Considering that as of September 2021, there are 3 agents that are FDA-approved for treatment of steroid-refractory GVHD, studies should clearly define in the inclusion and exclusion criteria what prior and/or concomitant therapies are allowed on the trial.

- During the Concept Development process, analyses should be performed to examine potential variables that may have an independent impact on the outcomes in question. If variables are not identified, adjustments may not be required. If variables are identified, a plan to accommodate or adjust for these effects should be incorporated into the analysis plan.

2.8. Pediatric Considerations

Children with chronic GVHD commonly present with skin, oral, liver, GI, eye, or systemic disease leading to failure to thrive, persistent immunodeficiency, or chronic pulmonary disease. Chronic "eczema" or dry skin are common manifestations of mild chronic GVHD of skin. Liver disease can present as asymptomatic hyperbilirubinemia or elevated alkaline phosphatase. As children can have marked elevations in alkaline phosphatase during growth spurts, children with this laboratory abnormality, a fractionated alkaline phosphatase should be obtained to confirm that the source is from liver and not from bone before a diagnosis of chronic GVHD is made. Children with chronic GVHD of the upper GI tract may have chronic anorexia or poor growth due to malabsorption. Rather than losing weight, children may 'fall off' their growth curve with decreased gains in height or weight velocity. In children < 2 years of age, this may also affect growth of head circumference. In addition to increasing the risk of opportunistic infection, the immunodeficiency or immune dysregulation associated with chronic GVHD can lead to GI dysfunction, malabsorption, low IgG (due to protein losing enteropathy), lactose deficiency, and failure to thrive.

2.9. Data Audits

Auditing will take place in accordance with BMT CTN guidelines. For BMT CTN studies in which chronic GVHD is the primary or major secondary endpoint, centralized pathologic review is encouraged.

3. TABLE A. GVHD SYNDROMES AFTER ALLOGENEIC HCT

Category	Onset of symptoms after HCT or DLI	Presence of acute GvHD features	Presence of chronic GvHD features
Acute GvHD			
Classic acute GvHD	≤ 100 days	Yes	No
Persistent, recurrent, or late-onset acute GvHD	> 100 days	Yes	No
Chronic GvHD			
Classic chronic GvHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

4. TABLE B. SIGNS AND SYMPTOMS OF CHRONIC GVHD

Organ or Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GvHD)	**Distinctive** (seen in chronic GvHD, but insufficient alone to establish a diagnosis)	**Other Features** (can be recognized as part of chronic GvHD if diagnosis is confirmed)	**Common Features** (seen with both acute and chronic GvHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculop apular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting, or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric)		
Scalp and body hair		• New onset of scarring or non- scarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse, or dull (not explained by other causes) • Premature gray hair	
Mouth	• Lichen-planus like changes	• Xerostomia • Mucocele • Mucosal atrophy • Pseudomembranes • Ulcers		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eyelids with edema)	
Genitalia *Females* *Males*	• Lichen planus-like features • Lichen sclerosus-like features • Vaginal scarring or stenosis • Phimosis or urethral/meatus scaring or stenosis	• Erosions • Fissures • Ulcers		

Organ or Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GvHD)	**Distinctive** (seen in chronic GvHD, but insufficient alone to establish a diagnosis)	**Other Features** (can be recognized as part of chronic GvHD if diagnosis is confirmed)	**Common Features** (seen with both acute and chronic GvHD)
GI tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea, vomiting • Diarrhea • Weight loss • Failure to thrive
Liver				• Total bilirubin, ALP >2 x ULN ALT> 2 x ULN
Lung	• Bronchiolitis obliterans diagnosed lung biopsy • Bronchiolitis obliterans syndrome*	• Air trapping and bronchiectasis on chest CT	• Cryptogenic organizing pneumonia** • Restrictive lung disease**	
Muscles, fascia, joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis	• Edema • Muscle cramps • Arthralgia or arthritis	
Hemato poietic and immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • AIHA and ITP • Raynaud's phenomenon	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

5. TABLE C. NIH GLOBAL SEVERITY SCORING

Mild chronic GVHD	1 or 2 organs involved with no more than score 1 plus Lung score
Moderate chronic GVHD	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
Severe chronic GVHD	At least 1 organ with a score of 3 OR Lung score 2 or 3
Key points: 1. In skin: higher of the two scores to be used for calculating global severity 2. In lung: FEV1 is used instead of clinical score for calculating global severity 3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity 4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score)	

6. TABLE D. CHRONIC GVHD ACTIVITY ASSESSMENT – CLINICIAN ASSESSMENT (FORM A)

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings:

0=none
1= mild
2=moderate
3=severe

Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — **Most severe cGvHD symptoms possible**

Over the <<time>> would you say that this patient's cGvHD is
+3= Very much better
+2= Moderately better
+1= A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
								Total score for all mucosal changes	

Gastrointestinal-Esophageal
- Dysphagia OR Odynophagia

0= no esophageal symptoms
1=Occasional dysphagia or odynophagia with solid food or pills during the past week
2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week
3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week

Gastrointestinal-Upper GI
- Early satiety OR
- Anorexia OR
- Nausea & Vomiting

0= no symptoms
1=mild, occasional symptoms, with little reduction in oral intake during the past week
2=moderate, intermittent symptoms, with some reduction in oral intake during the past week
3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week

Gastrointestinal-Lower GI
- Diarrhea

0= no loose or liquid stools during the past week
1= occasional loose or liquid stools, on some days during the past week
*2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion*
*3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)		TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min		Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

Shoulder

❑ Not done

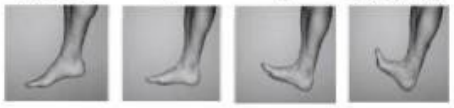
Elbow

❑ Not done

Wrist/finger

❑ Not done

Ankle



❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

7. TABLE E. CHRONIC GVHD ACTIVITY ASSESSMENT – PATIENT SELF REPORT

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

8. TABLE F. THE LEE CHRONIC GVHD SYMPTOM SCALE

Skin		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
1.	Abnormal skin color	0	1	2	3	4
2.	Rashes	0	1	2	3	4
3.	Thickened skin	0	1	2	3	4
4.	Sores on skin	0	1	2	3	4
5.	Itchy skin	0	1	2	3	4
Eyes and Mouth		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6.	Dry eyes	0	1	2	3	4
7.	Need to use eye drops frequently	0	1	2	3	4
8.	Difficulty seeing clearly	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain	0	1	2	3	4
10.	Ulcers in mouth	0	1	2	3	4
11.	Receiving nutrition from and intravenous line or feeding tube	0	1	2	3	4
Breathing		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12.	Frequent cough	0	1	2	3	4
13.	Colored sputum	0	1	2	3	4
14.	Shortness of breath with exercise	0	1	2	3	4
15.	Shortness of breath at rest	0	1	2	3	4
16.	Need to use oxygen	0	1	2	3	4
Eating and Digestion		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17.	Difficulty swallowing solid foods	0	1	2	3	4
18.	Difficulty swallowing liquids	0	1	2	3	4
19.	Vomiting	0	1	2	3	4
20.	Weight loss	0	1	2	3	4
Muscles and Joints		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21.	Joint and muscle aches	0	1	2	3	4
22.	Limited joint movement	0	1	2	3	4
23.	Muscle cramps	0	1	2	3	4
24.	Weak muscled	0	1	2	3	4
Energy		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25.	Loss of energy	0	1	2	3	4
26.	Need to sleep more/take naps	0	1	2	3	4
27.	Fevers	0	1	2	3	4
Mental and Emotional		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28.	Depression	0	1	2	3	4
29.	Anxiety	0	1	2	3	4
30.	Difficulty sleeping	0	1	2	3	4

9. TABLE G. RECOMMENDED CHRONIC GVHD-SPECIFIC CORE MEASURES FOR ASSESSING RESPONSE IN CHRONIC GVHD TRIALS

(Lee et al BBMT 2015)

Measure	Clinician Assessed	Patient Reported
Assessments	NIH Skin Score (0–3) NIH Eye Score* (0–3) Modified OMRS (0–12) Total bilirubin (mg/dL), ALT (U/L) Alkaline phosphatase (U/L) FEV-1 (liters, % predicted) NIH Joint Score (0–3) P-ROM (4–25)	N/A
Symptoms	NIH Lung Symptom Score (0–3) Upper GI Response Score (0–3) Lower GI Response Score (0–3) Esophagus Response Score (0–3)	Lee Symptom Scale [7] (0–100) Skin itching (0–10) Mouth sensitivity (0–10) Chief eye complaint (0–10)
Global rating scales	None–mild–moderate–severe [7] (0–3) 0–10 severity scale [8] (0–10) 7 point change scale [9] (−3 to +3)	None–mild–moderate–severe [7] (0–3) 0–10 severity scale [8] (0–10) 7 point change scale [9] (−3 to +3)

OMRS indicates Oral Mucosa Rating Scale.
* Components include both signs and symptoms.

10. TABLE H. RESPONSE DETERMINATION FOR CHRONIC GVHD CLINICAL TRIALS BASED ON CLINICAL ASSESSMENTS

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified Oral Mucosa Rating Score 0 after previous involvement	Decrease in NIH Modified Oral Mucosa Rating Score of 2 or more points	Increase in NIH Modified Oral Mucosa Rating Score of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of one or more	Decrease by 50%	Increase by 2x ULN
Lungs	-Normal %FEV1 after previous involvement -If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	-Increase by 10% predicted absolute value of %FEV1 -If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	-Decrease by 10% predicted absolute value of %FEV1 -If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and Fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least one measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0–10 scale	Clinician overall severity score increases by 2 or more points on a 0–10 scale