SUPPLEMENTARY APPENDIX

# Prospective international validation of the Quality of Life in Myelodysplasia Scale (QUALMS)

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**SUPPLEMENT**

*Instrument Development Details*

In 2011, using the guidelines for QOL instrument development outlined by Guyatt and associates,[1] and working with the FDA recommendations for developing patient-reported outcome measures,[2] we first conducted a series of focus groups with MDS patients and healthcare providers at Dana-Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH) in Boston, MA. The purpose of the groups was to explore and identify the most important MDS-related QOL factors, and how we could best capture those factors in a questionnaire. We provided the physicians who regularly treat patients with MDS at the DFCI and BWH with a list of the patients they had seen over the previous 3 months and asked which patients and caregivers would be comfortable in a group setting. Patients had to be $\geq$ 18 years old, have biopsy-proven MDS (WHO 2008 criteria),[3] and be able to communicate in English.

The selected 23 patients and their caregivers (if they had one) were then sent an invitation by regular mail (including a letter outlining the study goals, and an "opt-out" card) inviting them to participate in a focus group session. We accepted 9 patients (plus their 6 caregivers) on a first come, first served basis: of the remaining patients, 5 were willing to participate but had a scheduling conflict, 4 were put on a waitlist, and 5 never responded. The participating patients' median age was 73; there were 6 males and 3 females. Two were being observed without treatment, 3 receiving hypomethylating agents, 1 receiving only red cell transfusions, 4 receiving erythropoiesis-stimulating agents (ESAs; 2 as their only treatment), and 1 had undergone HCT. All BWH and DFCI physicians and non-physician health care providers who regularly treat patients with MDS were also invited to participate via email: we recruited 7 of the 8 physicians, and 10 other providers including 4 oncology nurses, 1 advanced practice nurse, 2 physician assistants, 2 social workers and an MDS patient advocate.

Through individual focus groups with these 32 members of the DFCI/BWH MDS community and using a clinical impact method of instrument development,[4] the three groups identified 12 preliminary MDS-relevant QOL domains and 60 potential question topics. Next, in a combined session following a

period of focused discussion, all participants ranked each domain from 1 (most important) to 12 (least important). As previously reported,[5] the most important domains were fatigue (1.4) and emotional health (3.3), and none of the 12 was ranked significantly differently by patients/caregivers versus physician/other MDS providers. We also asked each participant to rate the potential question topics as either "critical = 3," "important = 2," or "less important = 1" for MDS patients.

We next generated a draft instrument. Each question topic was assigned to one or more preliminary domains based on how broadly it touched upon the QOL of MDS patients and by referencing notes and audiotapes from the focus groups. We allocated a higher number of questions to the more highly-ranked preliminary domains, including six questions for each of the top two domains, five questions for each of the domains ranked #3 and #4, etc. This method created a 31-item preliminary instrument (many question topics fit more than one domain), to which we added the 7 most highly-ranked remaining question topics specific to MDS, independent of domain.

The 38-item draft QUALMS was next piloted with a new cohort of MDS patients at DFCI (n=20). We contacted consecutive patients with MDS with an upcoming appointment who were ≥ 18 years old, had biopsy-proven MDS (WHO 2008 criteria), and were able to communicate in English. Those consenting to participate (20/33= 61%) had an appointment arranged after their clinic visit to fill out the draft QUALMS (with observed behavioral coding), followed by a structured cognitive interview using a method based on Jobe's framework for assessing cognitive and social-motivational processes.[6] We reassessed after every four interviews, refining the QUALMS accordingly.

As a result of the piloting, five levels of response were chosen for each question (Never, Rarely, Sometimes, Often and Always), the reference time was optimized to be during the prior week, the wording of several questions was improved, five were given an opt-out option, and those opt-out questions were re-located to the end of the instrument. In the cognitive testing cohort, the median age was 76, and there were 13 males and 7 females. The mean time to complete the instrument was 7.5 minutes. Of note, no patient felt that any question should be removed, even if not relevant to him or her specifically. At the end of the

cohort, saturation was achieved, such that the final four patients agreed that none of the edited questions were "confusing," "upsetting," "irrelevant," or "intrusive."

*Validation Study Participants*

Subjects came from five MDS centers: Columbia University Medical Center in New York, New York, USA; Dana-Farber Cancer Institute in Boston, Massachusetts, USA; two centers affiliated with the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) in Rome and Cagliari, Italy; Moffitt Cancer Center in Tampa, Florida, USA; and Odette Cancer Center in Toronto, Ontario, Canada. Each institution obtained study approval from its respective institutional review board before enrolling patients, and all enrolled patients signed informed consent.

*Validation Study Measures and Outcomes*

**MDS-specific QOL** was measured using the finalized QUALMS as developed above, which consists of 38 items, answered on a 5-point scale ranging from "Never to Always." To score the scale answers were assigned a value with a potential range of 0 (worst) to 100 (best) as follows: Never = 100; Rarely = 75; Sometimes = 50; Often = 25 and Always = 0. Four items were reverse questions that were scored in the opposite direction such that Always = 100 and Never = 0. The QUALMS total score was calculated by averaging the scores on items 1 to 33, so the potential range of scores was 0 (worst) to 100 (best). Additionally, 5 single items (questions 34 to 38) that are clinically important but do not apply to all patients (e.g., "afraid of losing your job") were not included in the total scale score. Of note, for these questions, patients have the specific option to indicate each is "not applicable."

**General cancer-related QOL** was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[7] The QLQ-C30 consists of 30 items that ask respondents to indicate how often they experience a symptom (*e.g.*, pain) on a 4-point scale ranging from "not at all" to "very much." The QLQ-C30 is composed of both multi-item scales and single-item measures; given the multi-item nature of the QUALMS, we chose to compare only the QLQ-C30 multi-item scales. As anemia is a frequent presenting symptom and fatigue is the hallmark of MDS, **anemia-related QOL** was measured using the Functional Assessment of Cancer Therapy Anemia scale

(FACT-An),[8] a 47-item self-report measure consisting of the 27 core items from the FACT-G and 20 items that are unique to anemia, yielding three possible scores: AnS (anemia subscale), Fact-An total score (FACT-G + AnS) and a Trial Outcome Index (TOI; the physical and functional well-being subscales of the FACT-G +AnS).

Several **clinical measures** were also captured at baseline and follow-up, including WHO MDS subtype, hemoglobin (Hb), ANC, platelets, transfusion-dependence (using WHO criteria),[9] hospitalizations, transformation to AML, comorbidities using standard definitions,[10, 11] and current treatments (including HCT).

*Validation Study Design*

At each site, a research assistant recruited patients after reviewing the daily schedule of the participating physicians. Patients had to be ≥ 18 years old, have biopsy-proven MDS (WHO 2008 criteria), not have had a HCT or progressed to AML as of the baseline assessment, and be able to communicate in English for the American and Canadian centers. The QUALMS was also translated into Italian (for the GIMEMA centers) following standard translation and validation procedures.[12] Briefly, translation followed a forward-backward procedure, independently carried out by two native-speakers of the target languages (English and Italian); discrepancies were arbitrated by a third independent consultant. A final report providing a description of all translation and cultural adaptation decisions was also generated.

At the baseline visit patients completed the QUALMS, the QLQ-C30, and the FACT-An. Patients completed these at the clinic or hospital and were not allowed to take the instruments home. Instruments were completed on paper, and patients were encouraged to complete them without the assistance of caregivers. Patients were enrolled consecutively over nine months. QOL data and medical record information was entered into a centralized data system. At a subsequent appointment at least 3 months but not more than 6 months after enrollment (QOL in MDS has been shown to be mostly stable over this period),[13] patients again filled out the QUALMS, the QLQ-C30, and the FACT-An.

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