# Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial

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## ADDITIONAL MATERIALS

1. **STATISTICAL ANALYSIS PLAN**
2. **STUDY PROTOCOL**

This document describes the statistical approach developed prior to data analysis. This document supplements and updates the study protocol.

## 1. Introduction

Patients with advanced cancers commonly experience symptoms related to disease and treatment that can impact functioning and health status. Evidence suggests that clinicians frequently miss or underestimate the severity of patients' symptoms. Development of systems to identify symptoms and flag them for clinicians may enhance existing approaches to monitoring and managing symptoms, leading to improved outcomes. Prior research has demonstrated that systematic electronic collection of patient-reported symptoms can provide actionable information for providers, and inspires clinical actions such as counseling and medication changes. But there is limited evidence regarding whether this translates into benefits in how patients feel, function, or survive.

## 2. Study objective

To assess the impact of patient symptom self-reporting on clinical outcomes during chemotherapy for advanced cancers.

## 3. Study design

This is a randomized controlled trial comparing patient symptom self-reporting vs. usual care, with analysis plan endpoints including health-related quality of life (HRQL; main outcome), emergency room and hospital visits, overall survival, quality-adjusted survival, and nursing responses to email symptom alerts.

The study was approved and monitored by the MSKCC IRB. Through a limited IRB waiver, subjects potentially meeting eligibility criteria were identified in the electronic medical chart. These subjects were approached in clinical waiting areas and invited to participate. All participants underwent informed consent. Signed consent documents were submitted to and stored at MSKCC. The trial was registered by MSKCC at ClnicalTrials.gov.

## 4. Description of intervention and control

As described in the study protocol, patients in the intervention arm were invited to self-report selected symptoms from the NCI's CTCAE at all medical oncology clinic visits during study participation, via tablet computers or kiosks. This was performed using a previously developed/tested/published web questionnaire system called STAR ("Symptom Tracking and Reporting"). Computer-experienced patients were additionally given remote access to the STAR system, and received automated email suggestions to login and self-report. STAR triggered automated emails to nurses each time a patient-reported a symptom grade $\geq$3 or

worsened from prior. Control patients received “usual care”, consisting of the standard approach to symptom assessment and management at MSKCC: discussions between patients and clinicians at visits, and ad hoc telephone calls between visits. No specific direction was given to patients or clinicians about how to conduct usual care, or about how to manage symptoms. Participants remained on study until death, discontinuation of cancer treatment (e.g., transfer to hospice care), or voluntary withdrawal.

**5. Outcomes**

The initial protocol focused primarily on HRQL using data from the EuroQoL EQ-5D questionnaire, administered to participants approximately every 3 months plus/minus 1-2 months due to heterogeneity in follow up times between patients in real world treatment contexts. ER/hospitalization endpoints were subsequently added to the analysis plan using data from hospital records. Quality-adjusted survival was envisioned using EQ-5D data with survival time, and overall survival was subsequently added based on SSDI and hospital record data. Chemotherapy dose reductions were initially included in the protocol but removed from the analysis plan due to poor data quality from medical chart abstraction. Nursing responses to email alerts were included using data from prospectively collected nursing forms.

The main HRQL analysis is specified to occur at the 6-month time point (i.e., 6 months following enrolment for each patient). This timing was envisioned to allow sufficient time for patient involvement on the study, but was anticipated to occur before substantial attrition due to death, hospice, or discontinuation of care. To account for missing data, an approach using the Last Observation Carried Forward (and sensitivity analyses using various other imputation methods) will be used for patients without HRQL data at 6 months, as described below. Analyses will include comparisons of means between study arms, as well as responder analyses (comparisons of proportions with change from baseline between arms), the latter which have become of increased interest in PRO analyses since the initial protocol was designed. Research published subsequent to development of the protocol reports that a 6-point change in EQ-5D score is clinically meaningful to patients, and the analysis will assess differences in changes of this magnitude between study arms.

Survival, quality-adjusted survival, and ER/hospital visits will be analyzed at 1 year, with follow-up time to allow for 1-year assessments across the population. This timing was selected based on institutional data suggesting that approximately 30-40 percent of the population would have died by this time point, and an assertion that 1-year is clinically reasonable and feasible as a time frame to measure the impact of a symptom monitoring intervention. The approaches to quantifying quality-adjusted survival and ER/hospitalization are described below.

**6. Population and subgroups**

Per protocol, patients were eligible if they were commencing any line of outpatient systemic chemotherapy for an advanced/metastatic cancer at Memorial Sloan-Kettering Cancer Center, specifically for breast, genitourinary, gynecologic, or lung cancer. Breast cancer was not

included in the initial protocol but was subsequently added through amendment. Participants had to be able to read and understand English, and have ECOG PS $\leq$2. Following consent, participants were divided into two subgroups based on level of computer experience. "Computer-experienced" participants had prior/outside access to the web and email, and vice-versa for "computer-inexperienced" participants. These subgroups were independently randomized to the intervention vs. usual care.

**7. Statistical analysis procedures**

a) Analyses of baseline patient characteristics: Baseline covariates including age, sex, race, cancer type, and education will be compared between study arms (STAR vs. usual care) using Fisher's exact tests for categorical variables and t-tests for continuous variables. This approach will be used for the overall study group, and within each prespecified subgroup (computer inexperienced and experienced). These same procedures will also be used to compare baseline characteristics between the two subgroups (i.e., computer experienced vs. inexperienced).
b) Analysis of health-related quality of life: The proportion of participants experiencing better or worse EQ-5D scores will be compared descriptively and using Fisher's exact test. Change in mean EQ-5D scores from baseline to 6 months will be compared between arms (both overall and within each subgroup) using t-tests, univariable and multivariable linear regression models. For the univariable analysis in the overall population, subgroup will be included as a variable to control for potential effects of computer experience. For the multivariable models, covariates will include all baseline characteristics (listed above). Effect sizes will be calculated as the difference in means between study arms divided by the common standard deviation.
c) Analysis of overall survival at 1 year: Survival data are derived from national indices with complete survival follow up data at one year (i.e., no censoring). Assuming no censoring, the percentages and 95% confidence intervals of patients alive at one year will be reported by arm (both overall and within each subgroup) and compared using univariable and multivariable logistic regression models. For the univariable analysis in the overall population, subgroup will be included as a variable to control for potential effects of computer experience. For the multivariable models, covariates will include all baseline characteristics (listed above). If censoring occurs, time to event analysis will be done using Cox regression models.
d) Analysis of quality-adjusted survival at one year: Quality adjusted life months (QALMs) will be calculated at the patient level by multiplying average EQ-5D scores by survival times for each EQ-5D reporting interval during the initial year of enrollment. These values will be summed to yield a total number of quality-adjusted life months for that patient during that year. QALMs will be compared between arms (both overall and within each subgroup) using univariable and multivariable linear regression models. For the univariable analysis in the overall population, subgroup will be included as a variable to control for potential effects of computer experience. For the multivariable models, covariates will include all baseline characteristics (listed above).

e) Time to initial emergency room (ER) visit: For any given participant, the time to the initial ER visit (regardless of whether still on study) will be calculated from enrollment date. Death is treated as a competing event. If no events or death occur, patients will be censored at the end of the study period. Time to first ER visit will be compared between arms (both overall and within each subgroup) using univariable and multivariable competing risk regression models. For the univariable analysis in the overall population, subgroup will be included as a variable to control for potential effects of computer experience. For the multivariable models, covariates will include all baseline characteristics (listed above).
f) Time to first hospitalization: The same approach will be employed as for ER visits.

**8. Handling of missing data**

For the primary HRQL analysis, patients with a missing baseline EQ-5D questionnaire will not be included. For patients with a missing EQ-5D questionnaire at the 6 month time point, in the primary HRQL analysis, Last Observation Carried Forward will be used, including any post-baseline values (i.e., if only baseline EQ-5D is available, it will not be carried forward in the primary analysis; see "Sensitivity analyses" below for an approach employing this method). Specifically, the EQ-5D value in closest proximity to 6 months that is prior to the 6-month time point will be used. If no post-baseline EQ-5D score is available prior to or at the 6-month time point, subsequent EQ-5D values may be considered if in relatively close proximity to 6 months.

**9. Sample size**

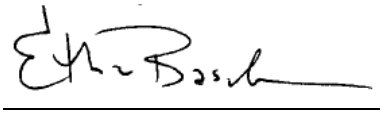
The study was designed to analyze the two subgroups based on computer experience both together and separately, with an assumption that approximately 30% of subjects would fall into the inexperienced category. The experienced group was randomized 1:1 and the inexperienced 2:1. The initial protocol specified 1:1 randomization in both subgroups which was subsequently modified based on interest of the investigators in the latter group, which is less common. As such, the initial protocol projected that 30-40% of participants would be computer-inexperienced, and it was estimated that with 150 participants in the web-inexperienced subgroup randomized 1:1 (75 per arm), there would be 80% power to detect an effect size of 0.46 (e.g., a 6-point difference in mean EQ-5D scores with a standard deviation of 13, or a 20-point difference with a standard deviation of 43) using a t-test with a two-sided alpha of 0.05. Prior to enrollment, the proportion of intervention to control participants was increased to 2:1 (150 to STAR and 75 to usual care) in the computer-inexperienced subgroup, which reduced (improved) the detectable effect size with 80% power to 0.40.

**10. Sensitivity analyses**

For the HRQL analyses, multiple sensitivity analyses will be run using different methods of imputation for missing data. These will include:

- Analyzing only scores available at 6 months (i.e., not using any observations carried forward).

- LOCF approach which includes baseline values carried forward for participants who do not report any EQ-5D scores subsequent to baseline.
- Average observation carried forward.
- Assigning an EQ-5D value of zero for patients who have died prior to reporting a 6 month EQ-5D score.



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# Pilot Study of *STAR*, an Internet-based System for Cancer Patients to Self-report Toxicity Symptoms, Performance Status, and Quality of Life

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Note: All Investigators and Consenting Professionals have been certified in Human Subjects Research.

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## 1.0 PROTOCOL SUMMARY

Monitoring of symptoms and performance status during chemotherapy is a cornerstone of medical oncology routine care, and is standard for patients enrolled in clinical trials. As patients experience various adverse effects, their needs for therapy alteration, supportive care, or informational services often change.

This pilot study will assess patient use of STAR (Symptom Tracking and Reporting for Patients), an online system designed for cancer patients to self-record toxicity-related symptoms based on NCI *Common Terminology Criteria for Adverse Events v3.0*, performance status by ECOG criteria, and global quality of life by the EuroQOL 5-D assessment tool. Secondary outcomes will include patient assessment of the usefulness of STAR, clinician perceptions of the potential value of STAR in routine clinical practice, and an evaluation of whether STAR improves the patient experience of care as assessed by quality of life and satisfaction measures.

In an evaluation of feasibility, patients with gynecologic malignancies beginning new chemotherapy regimens will be recruited from MSKCC outpatient clinics until at least 80 subjects with each cancer type are enrolled (of which at least 25% do not have home Internet access). Enrollees will be encouraged to login to STAR at clinic visits using waiting-area computers. Those with home Internet access will also be able to login to STAR remotely at any time. Entered information will be stored in a secure database located on a firewall-protected MSKCC server. In a separate evaluation of the impact of STAR on patient QoL and satisfaction, patients accrued from the MSKCC lung, prostate, gastrointestinal or gynecologic medical oncology clinics will be randomly assigned to receive clinic-only plus home STAR access vs. no STAR access (standard care).

Based on information entered into STAR and recorded in the database, it will be possible to generate summary STAR Reports which track symptom trends over time for each patient. When an enrolled patient has a clinic appointment during the study period, a STAR Report will be printed and added to other materials that are routinely reviewed by the nurse and/or medical oncologist as a part of standard care at MSKCC.

Any time an online questionnaire is submitted by a patient which includes a toxicity grade of 3 or 4, an automated email will be sent to the medical oncology fellow coordinating this study, as well as to a designated clinician in each respective service. They will contact the primary physician and/or clinic nurse with this information. The primary oncologist will have the option to receive a copy of this email as well. Patients will be informed that there is no regular monitoring of information entered into STAR, and that they should call their physician's office if they feel that they require medical attention. This will be emphasized to patients in the Informed Consent, during a STAR training session, and on the STAR website. In addition, anytime a patient enters a toxicity grade of 3 or 4 into STAR, a popup box will appear on the screen reminding them to consider calling.

Utilization of STAR will be tabulated by measuring how often each user accesses the system, when use occurs in relation to chemotherapy administration, and the sites of use (home versus clinic). In the feasibility analysis, we will consider the study results to suggest that STAR is a strategy warranting larger scale evaluation if among consenting subjects, half of those with home Internet access and one-third of those without home Internet access login to STAR at least once during the study period. Patient assessment of the usefulness of STAR will be measured via interim and exit questionnaires. Clinician perceptions of the potential value of STAR will be evaluated via an email survey and questions asked at a team meeting. In the randomization analysis, the impact of STAR on QoL and satisfaction measures will be considered clinically meaningful if there is a 20% improvement in mean scores.

## 2.0 OBJECTIVES AND SCIENTIFIC AIMS

### 2.1. Primary Objective:

To evaluate patient willingness to use STAR (Symptom Tracking and Reporting for Patients), an Internet-based system for cancer patients to self-report common toxicity symptoms, performance status, and quality of life.

### 2.2. Secondary Objectives:

a. To measure patient assessments of the usefulness of STAR, and to measure clinician perceptions of the potential value of STAR in routine outpatient cancer care.

b. To assess if STAR improves the patient experience of care as measured by quality of life (QoL), satisfaction, the number of calls between nurses and patients, or dose reductions.

## 3.0 BACKGROUND AND RATIONALE

### 3.1 Rationale for Patient Self-Monitoring during Chemotherapy:

The purpose of this pilot study is to clarify whether patients are willing to self-report common toxicity information, performance status, and quality of life using the STAR (Symptom Tracking and Reporting for Patients) system via the Internet. Feasibility will be assessed based on patient utilization rates of STAR. Patient assessment of the usefulness of STAR and clinician qualitative perceptions of the potential value of STAR will be measured via questionnaires adapted from validated instruments used in prior studies of information technology interventions and user satisfaction. If STAR is utilized and patient feedback is generally positive, future investigation will be considered reasonable in order to assess the potential value of STAR in routine care of cancer patients, and in the setting of clinical treatment trials.

Monitoring of symptoms and performance status during chemotherapy is a cornerstone of modern medical oncology practice, and is standard for patients enrolled in clinical trials (1-6). As patients experience various adverse effects, their needs for therapy alteration, supportive care, or informational services often change (7). There is limited available information about the feasibility or effects of allowing cancer patients to record their own symptoms through the use of electronic interfaces such as the Internet.

As healthcare delivery becomes progressively dependent on information technology, institutions like MSKCC face choices about creating or purchasing systems for clinical communication with patients, nurses, and physicians. Study of the value of systems like STAR (that aim to enhance patient-clinician communication, efficiency, accuracy, and patient satisfaction) may aid in these decision-making processes.

### 3.2 Patient Self-Assessment Systems:

Cancer patients commonly express an interest in shared decision-making and access to information towards treatment decisions (8-11). An electronic portal to record symptoms allows patients to enter information at the time of clinic visits (point-of-care), or at any time between clinic visits using a computer with Internet access (home, library, office, etc).

Point-of-care data entry may provide several benefits over conventional clinician-collected toxicity information: Patient self-reporting may save clinicians time, increase accuracy and depth of information, foster discussion with clinicians, and improve patient satisfaction with visits. Patient reporting of symptom-changes between visits may provide an overview of the patient experience throughout chemotherapy cycles. More appropriate regimen adjustments or supportive care choices may be possible using this information, even if no clinician rapid-response system is implemented.

Real-time electronic reporting also affords an opportunity to increase the response time of Investigators to severe toxicities, which may have particular relevance in multicenter early-phase trials with small numbers of enrollees at each institution. Recent attention has been given to the development of rapid reporting systems for early detection of toxicities in clinical trials (12;13). Electronic reporting and self-assessment of symptom-based toxicities may contribute to the improvement of early detection systems.

Computer-based informational resources produce higher patient satisfaction and superior knowledge transfer than print information (14;15). Patients prefer computer systems that provide access to their own personal health record to systems that only provide general health information (15).

Patient self-reporting of information using electronic interfaces is increasingly used in research and clinical settings, although study of its use is limited (16-20). For example, feasibility has been demonstrated for the collection of quality of life/utility information (16), pain indices (17), home-measured blood glucose levels (21), alcohol use (19), and excess bleeding (20). Interfaces have included email, customized web pages, handheld computers, cellular telephones, short messaging services (SMS), and two-way pagers.

Levels of compliance have been high overall in available studies. In a patient population with chronic pain, compliance with an electronic diary to record daily pain scores was 94% (17). User-acceptance was similarly high in an outpatient breast cancer population at the Dana-Farber Cancer Institute, which self-entered health-related quality of life data into a handheld computer (16). High patient satisfaction was noted with the use of electronic blood-glucose reporting in gestational diabetes (22). In a study of telephone-based electronic information assessment of alcohol use, with information placed into the patient record prior to clinic visits, clinicians universally were satisfied with the system, and believed that their practices were changed in a positive way (19). Independent verification

revealed a 15% increase in detection of alcoholism through use of this surveillance system.

Although there is little study in cancer patients, there are examples in practice of computer-based symptom tracking systems. For example, the West Clinic, a large oncology private practice in Memphis, TN has developed a "Patient Care Monitor" system. Each clinic visit, patients enter symptom information into a database via a wireless tablet-PC. This information is transmitted to clinicians for real-time use during clinic visits, and becomes a part of the medical record. This system does not track common toxicity criteria, quality or life, or performance status, and has not been evaluated systematically.

A group at the University of Utah has evaluated the feasibility of using telephone-linked care (TLC) for monitoring symptoms in 27 cancer patients receiving chemotherapy (23). This system is similar to TLC applications that have been used to follow symptoms in patients with COPD (24) and other chronic diseases (25-28). The majority of patients were white (92%) and women (69%); mean age was 54 years with greater than 16% older than 65; most subjects had breast cancer (60%) with the balance made up of seven other cancers; most patients had advanced disease (60%) and were not working (77%). Measured symptoms included: "fatigue, trouble sleeping, nausea/vomiting, feeling blue, anxiety/nervousness, sore mouth, and fever." Participants were instructed to call a central telephone number daily and number-punch responses to questions measuring presence/severity of symptoms. The system took 10 minutes to learn on average, and was rated as "easy to learn" by 89% of subjects. At the study's end, 18 patients were available for exit questionnaires, which determined that 61% found that TLC helped them keep track of symptoms, 67% felt the system aided them in knowing which symptoms to discuss with physicians, 57% believed the system reminded them to call their physician with concerns, and 50% felt the TLC system sounded like a conversation with a doctor or nurse. Of interest, only 43% of respondents felt that TLC helped them feel they were participating in their own care. The authors are currently designing a study to assess the effects of an expanded TLC system that sends alerts to clinicians and tracks participant responses over time. This system does not track common toxicity data, quality or life, or performance status, and is not linked to the conduct of clinical trials.

### 3.3 Interactive Health Communication:

Interactive health communication (IHC) is an emerging field which encompasses the development, implementation, and study of electronic communication technologies, and the impact of these technologies on disease outcomes, patient/clinician satisfaction, communication/knowledge transfer, safety, system efficiency, and cost (29). As healthcare delivery becomes progressively dependent on information technology, institutions face choices regarding which systems to purchase, develop, or implement.

The impact of IHC on patient satisfaction is not well understood, and is an area identified by the Office of Disease Prevention and Health Promotion of the U.S. Department of Health and Human Services (HHS) as needing further evaluation (29-31). Commonly used measures include questions regarding patients' confidence in their clinicians, perceived availability of clinicians, frequency of use, and patient satisfaction with systems. In a 1999 report by the Science Panel on Interactive Communication and Health, HSS, five levels of evaluation are proposed for the assessment of IHC applications (Table 1) (29). This report cites several potential benefits of such evaluation, including "improved quality, utility, and effectiveness… reduction of likelihood of harm… better use of resources for effective applications… greater participation of stakeholders in the development and implementation process… [and] improved decisions about applications."

**Table 1: Five Levels of IHC Evaluation (29)**

| Level of Evaluation | Key Evaluation Questions |
|---|---|
| Level I: Engagement and Appeal | Did the users like the application? |
| Level II: Learning | Did users' knowledge, skills, and attributes improve? |
| Level III: Behavior Change | Did users change their behaviors? |
| Level IV: Impact | Did the application have any benefits? |
| Level V: Return on Investment | Did the benefits of the application exceed its cost? |

There is increasing demand to provide patients with access to their own clinical information online, using systems such as the New York Presbyterian Hospital *Patient Clinical Information System* (PatCIS) or Partners Healthcare System *Patient Gateway*, that link patients via a secure website to personal information derived from a clinical data repository such as laboratory data, radiology reports, or the electronic medical record. Early research suggests that such access improves patients' understanding of their conditions, improves patient and clinician satisfaction, and may increase accuracy due to patient corrections of incorrect data (32;33).

The University of Wisconsin-Madison has developed the Comprehensive Health Enhancement Support System (CHESS), which provides home computers to patients with breast cancer or HIV/AIDS (34-40). This program was initiated in 1989. Users can access selected content (tutorials, decision analyses, supportive care information), ask questions of experts, monitor their own health record, read accounts of other patients, and join discussion groups. In a brief report of feasibility in 38 patients, average use was 6.8 times per week, with equivalent rates across ages (mean age 72 years) and stages of cancer (41). In a controlled assessment of this system, 246 women under age 60 were randomized to receive home access to CHESS versus no access (42). After two months of use, the CHESS group was significantly more competent at seeking information, more comfortable participating in care, and more confident in their doctors. Effects were greatest in women from underserved populations. The authors reported similar results of using the CHESS program in 204 HIV-infected patients, and

noted shorter time-per-visit to ambulatory care as well as less frequent and shorter hospitalizations compared to a control group (43).

The University of Wisconsin has recently received a $10 million NCI award to establish a Center of Excellence in Cancer Communications, in order to assess (1) the effects of the CHESS program on breast cancer outcomes; (2) compare the effects of CHESS compared to general Internet access; and (3) evaluate whether CHESS impacts on patient-clinician information-sharing or improves palliative care.

### 3.4 Future Opportunities:

This pilot study of STAR represents an early step towards future research at MSKCC of Internet-based platforms for enhancing patient-institution communication, patient satisfaction, quality of care, and information efficiency. This is an area of intensifying research, and is of increased interest to the NIH and NLM: multiple RFAs/PAs have been issued in this area over the past two years, equaling more than $60M in federal grant funding.[†]

### 3.5 Computer and Internet Use among Patients:

Implementation and evaluation of an Internet-based tool for patients depends on the ability of patients to access and use a computer/the Internet. In order to characterize Internet use by MSKCC patients and their companions, we conducted an anonymous waiting-room survey of patients presenting to the general surgical and gastrointestinal oncology outpatient departments between December 1999 and February 2000 (unpublished data). Of the 625 individuals approached, 443 completed and returned questionnaires (223 patients and 220 companions). The mean age of patients was 59-years-old, and 43% were female. Colorectal cancer was the most common diagnosis (45%), followed by pancreatic/biliary (8%), gastro-esophageal (8%), hepatic (6%), sarcoma (5%), and endocrine (5%). Among the respondents, 64% of patients and 76% of companions owned computers, and Internet access was available at home to 58% and 68% respectively (Table 2).

**Table 2: MSKCC Survey Results (12/99 – 2/00)**

| | |
|---|---|
| Cancer patients with home computers | 64% |
| Companions of cancer patients with home computers | 76% |
| Cancer patients with home Internet access | 58% |
| Companions of cancer patients with home Internet access | 68% |

[†] Dynamic Assessment of Patient-Reported Chronic Disease Outcomes (RFA): http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-011.html; Innovations in Biomedical Computational Science and Technology (PA): http://grants1.nih.gov/grants/guide/pa-files/PAR-03-106.html; National Centers for Biomedical Computing (RFA): http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-003.html; Continued Development and Maintenance of Bioinformatics and Computational Biology Software (PA): http://www.bisti.nih.gov/bistic_funding.cfm; Centers of Excellence in Cancer Communications Research (CECCRS) (RFA): http://deainfo.nci.nih.gov/concepts/CA-03-007.htm.

In November-December 2003, we conducted an informal anonymous survey of 90 patients (30 with gynecologic malignancies, 30 with lung cancer, 30 with prostate cancer) in waiting-areas f the MSKCC outpatient clinics and showed these individuals a paper version of the STAR questionnaire (Table 3). Ages ranged from 40 to 84. The majority of patients noted regular access to the Internet. All patients without regular access to a computer or the Internet were older than 75 years, whereas all patients younger than 75 years had regular access. Of the patients who used the Internet, one patient used the Internet at a library, all others at home. All patients with home access expressed interest in electronic symptom self-tracking. When shown a demonstration of STAR, all patients with Internet experience stated they would be interested in regularly using STAR.

When shown a paper version of the STAR questionnaire, including CTCAE toxicity criteria converted into patient language for seven common s (nausea, vomiting, diarrhea, constipation, pain, fatigue, dyspnea), criteria for ECOG performance status, and the EuroQOL 5-D quality of life assessment (Appendix 4), all 90 patients understood the language of the questions and answered all questions without difficulty.

**Table 3: Informal MSKCC Survey of 90 Outpatients (11-12/03)**

| | GYN | LUNG | PROSTATE |
|---|---|---|---|
| Do you have regular access to a computer (home, library, other)? | 83% | 68% | 83% |
| Do you use the Internet regularly? (If not, is there somebody at home who does?) | 73% (50%) | 65% (56%) | 70% (60%) |
| Do you use email? | 60% | 48% | 64% |
| Would you be interested in regularly using STAR to enter symptom information into an electronic diary over the Internet? | 80% | 70% | 88% |

In the United States overall, 2/3 of the population uses the Internet, 57% has home access, and 27% has a broadband connection (44;45). Use is greatest among individuals who are younger, more affluent, better-educated, and white, although use is increasing among those over 50 years-old and with incomes below $25,000 (Table 4).

**Table 4: Profile of U.S. Online Population (44)**

| AGE | U.S. Adults Online (%) | All U.S. Adults (%) |
|---|---|---|
| 18 – 29 | 28 | 22 |
| 30 – 39 | 23 | 22 |
| 40 – 49 | 23 | 20 |
| 50 – 64 | 24 | 18 |
| 65 + | 5 | 16 |
| **SEX** | | |
| Men | 49 | 48 |
| Women | 51 | 52 |
| **RACE/ETHNICITY** | | |
| White | 76 | 76 |
| Black | 12 | 12 |
| Hispanic | 9 | 10 |
| **EDUCATION** | | |
| High school or less | 37 | 52 |
| Some college | 31 | 26 |
| College graduate (or post graduate) | 32 | 22 |
| **HOUSEHOLD INCOME** | | |
| $25,000 or less | 18 | 25 |
| $25,001 - $50,000 | 25 | 29 |
| $50,001 and over | 46 | 32 |

Surveys suggest significant numbers of patients want to communicate with physicians via email (46;47) or over the Internet (48;49). More than one-third of patients ask clinicians about websites during visits (50), and consider use of the Internet to enhance the patient-physician relationship (51;52). Up to 85% of U.S. physicians regularly access the Internet, 63% use daily email, and 33-75% communicate with patients via email (53-58). Healthcare information remains a top reason that adults search the Internet, with over 100 million individuals seeking such content, annual growth rates up to 80%, and the highest rate of growth in those older than 65 years (57). However, less than half of consumers are satisfied with the online content provided by their health plans (59).

Despite a large number of informational web sites available for cancer patients (60), there is little opportunity for patients to use electronic resources to record their symptoms or concerns. For cancer patients receiving routing outpatient care, the development of resources such as STAR may allow for linking to more appropriate informational services, may foster better discussions with clinicians, save time, and inform better treatment decisions. For patients enrolled in chemotherapy trials, STAR may provide a more rapid and accurate way to detect severe symptom-based adverse events.

### 3.6 Toxicity Reporting for Patients in U.S. Cancer Clinical Trials:

In the United States, cancer patients enrolled in National Cancer Institute (NCI) sponsored treatment trials are routinely evaluated using NCI *Common Terminology Criteria for Adverse Events (CTCAE)*, formerly known as Common Toxicity Criteria (CTC), which are updated periodically (current version: 3.0, updated December 12, 2003) (61). CTCAE grading has been compared to patient

self-evaluations of symptoms for nausea and vomiting, and found to have greater agreement than other toxicity grading systems, such as the scale developed by the World Health Organization (4). However, CTCAE evaluation may not provide an accurate depiction of quality of life, suggesting the value of also assessing global quality of life and/or performance status in patients receiving cancer care (62).

CTCAE v3.0 includes 28 general classification categories, each divided into multiple individual adverse events (AEs). Each AE can be assigned a severity grade based on CTCAE specified criteria. An AE may be a symptom, unfavorable sign (abnormal laboratory value), or disease temporally associated with treatment. Although reporting of signs depends on evaluation by a clinician, the evaluation of symptoms (AEs such as nausea, pain, anxiety) depends largely on patient subjective reporting. Similarly, assessment of performance status or global quality of life relies on patient responses.

### 3.7 Toxicity Evaluation at MSKCC for Patients during Routine Care:

During routine care of MSKCC outpatients not enrolled in clinical trials, performance status and symptoms are assessed at clinic visits. Most often, this information is recorded on printed "Medical Oncology Visit Sheets" that provide space for clinician grading of 13 toxicity categories with common toxicity criteria (instructions) printed on the backs of these sheets (Figure 1). There is also a specific space for performance status. Clinicians (nurses, fellows, staff physicians) may fill out these sheets at the time of patient visits. The sheets are then optically scanned to become a part of the permanent electronic medical record (EMR). Descriptions of patient symptoms may also be included in the "review of systems," a discrete section of notes/dictations which is required to meet certain levels of billing requirements. Performance status may be added to the physical exam section of notes/dictations. Symptoms and performance status are often cited as reasons for starting, stopping, or altering therapeutic regimens, for adding supportive medications, or for addressing broader psychosocial issues.

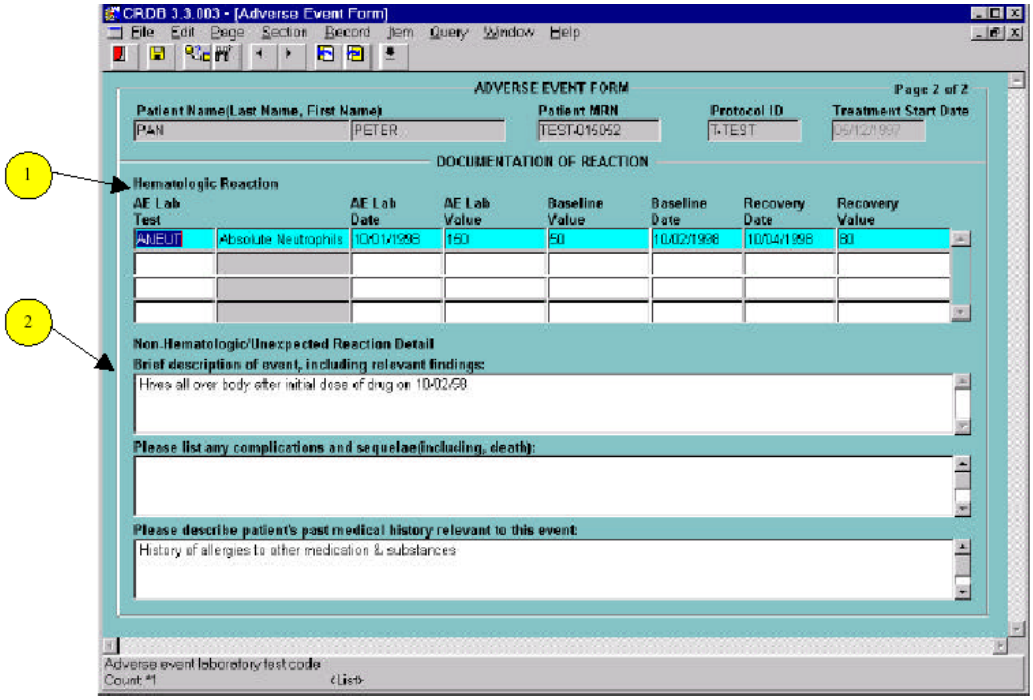
**Figure 1: MSKCC Common Toxicity Categories on Medical Oncology Visit Sheet**

| ASSESSMENT | DISEASE/ THERAPY | GRADE | | | | | INTERVENTION / OUTCOME |
|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | |
| Nausea | | | | | | | |
| Vomiting | | | | | | | |
| Diarrhea | | | | | | | |
| Constipation | | | | | | | |
| Stomatitis | | | | | | | |
| Pulmonary | | | | | | | |
| Neurosensory | | | | | | | |
| Skin | | | | | | | |
| Fatigue | | | | | | | |
| Fever | | | | | | | |
| Bleeding | | | | | | | |
| Urinary | | | | | | | |
| Other | | | | | | | |
| Pain | Intensity (0-10): | | | | | | Relief (Y/N): |

## 3.8 Toxicity Evaluation at MSKCC for Patients Enrolled in Chemotherapy Clinical Treatment Trials:

For patients enrolled in MSKCC IRB treatment protocols, clinical data (including common toxicity information) is maintained in the electronic Clinical Research Database (CDRB). Toxicity data using various scales is entered by Research Study Assistants (RSAs) into the CDRB, based on clinician assessment (Figure 2). Often, this information is extracted by RSAs from "Medical Oncology Visit Sheets" that have been filled out by nurses, fellows, or staff physicians (Figure 1). RSAs may also derive toxicity information from other aspects of the medical record. Collection and coding of common toxicity information by RSAs is time-consuming, and categories of toxicity are often absent from the available record, leading to incomplete reporting. Direct assessment by patients of common toxicities into an electronic system such as STAR could potentially save RSA data-entry time. It is not known how clinician and patient recorded assessments would compare, but it is logical to expect that patient self-reported severe toxicities would require clinician verification to maintain consistency.

**Figure 2: MSKCC CRDB Toxicity Reporting Form**
*Legend: 1=Type of Toxicity; 2=Optional Description of Toxicity*




## 3.9 Justification for Assessing STAR in Patients with Different Cancer Types

Assessment of usage patterns of STAR in patients with three different cancer diagnoses will yield more generalizable results (compared to assessment in only one cancer type), and allow us to better understand patient characteristics associated with adherence to electronic self-reporting. For example, lung cancer patients generally experience greater disease acuity with a predominance of respiratory symptoms and performance status compromise, and represent an older population with multiple comorbidities. Based on paper surveys conducted in MSKCC clinics in 2003, this population appears to be relatively less experienced with the Internet (Table 3). In contrast, prostate cancer patients tend to have a longer course of disease with symptoms often related to post-operative difficulties or hormonal treatment, and psychosocial issues related to sexual health, genitourinary function, and the specter of disease progression. The gynecologic oncology population presents a female counterpart to the all-male prostate cancer population, with a group at MSKCC which is relatively well-educated with prolonged disease courses, and frequent abdominal/gastrointestinal and genitourinary symptoms. Towards future research and technology implementations, it will be valuable to compare usage patterns between each patient cohort.

## 4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

The primary objective of this is study is to assess patient willingness to use STAR (Symptom Tracking and Reporting for Patients), an Internet-based system for self-tracking of common toxicities, performance status, and quality of life.

### 4.1 Development of STAR:

The STAR system has been developed at MSKCC as a collaboration between study Investigators in the Departments of Medicine, Epidemiology and Biostatistics (including members of its Computing Resource group who maintain the infrastructure of the CRDB), and Information Systems. The content of each STAR screen has been designed by the Investigators and is available for review in Appendix 1, or online at www.mskcc.org/star (username: tester3; password: tester3). This design consists of a homepage for patients to login to STAR, followed by screens containing questions to assess toxicity-related symptom information based on NCI *Common Terminology Criteria for Adverse Events v3.0* for up to 15 common symptoms (specific to the cancer diagnosis in each of the three disease cohorts, with items selected based on literature review and cooperation with clinicians in each disease management team), performance status by Eastern Cooperative Oncology Group (ECOG) criteria, and global quality of life (QoL) by the EuroQoL 5-D assessment tool (Appendix 4). An area for entry of free text comments about specific concerns or symptoms is provided ("patient journal").

The technical functionality of STAR has been developed and is maintained by software designers in Information Systems with collaboration from members of the Computing Resource Group in Epidemiology and Biostatistics. Security issues are described in Section 4.2.4, the logistics of logging into STAR in Section 4.2.5, and generation of STAR Reports for clinician use in Section 4.2.6. A diagram of the system architecture/server configuration is reproduced in Appendix 7.

The initial design of the symptom questionnaire includes a single scroll-down page on which all items are included in list form (Appendix 1, IIa). Based on feedback from an initial cohort of patients in the gynecologic oncology clinic, we may alter aesthetic aspects of the questionnaire to improve the user-friendliness of the interface when used in the prostate and thoracic oncology clinics. For example, the font size or screen-to-screen functionality may be altered (Appendix 1, IIb). However, the content, server architecture, and security/privacy specifications of the system will remain unchanged (Appendix 7). We will acknowledge any differences between the interfaces used in each clinic in the data analysis (Section 11.2).

## 4.2 Study Design:

### 4.2.1 Patient Accrual:

This pilot study will be undertaken in patients with gynecologic, gastrointestinal, lung, or prostate malignancies receiving primary oncology care in the MSKCC oncology outpatient clinics, who are starting a new chemotherapy regimen (or hormonal therapy in the case of prostate cancer patients only) not on a clinical trial. Justification for the choice of these four cancer types is discussed in Section 3.9. For the non-randomized feasibility analysis in the gynecologic oncology clinic (Objectives 2.1 and 2.2a), an accrual period will remain open until at least 80 patients with each cancer type are enrolled (including at least 25% without home Internet access). For the separate randomization analysis in the gynecologic, gastrointestinal, lung, and prostate cancer clinics (Objective 2.2b), accrual will continue until approximately 150 patients with prior web/email experience and 150 patients without prior web/email experience are enrolled (detailed in Section 4.2.8).

### 4.2.2 Study Period:

For each patient, we will define a minimum study interval of 8 weeks beginning on the day of initiating a new chemotherapy regimen subsequent to enrollment, lasting up to one year.

### 4.2.3 Patient Training Sessions:

At the time of enrollment, each subject will undergo a 5-20 minute training session for the STAR system on an Internet-enabled computer. This training session will be conducted by Ethan Basch MD, Dorothy Dulko NP, or a designated RSA/session assistant using a computer located in a private patient computing area on the 6$^{th}$ or 9$^{th}$ floor of the MSKCC 53$^{rd}$ street outpatient clinic building, or on a private computer in the waiting area of the 3$^{rd}$ floor of the Kimmel Center. Training will include:

- Provision of a unique username/password and URL for STAR.
- Instruction how to navigate to the STAR data entry frontpage using the Internet.
- Instructions how to login to STAR, enter personal information about toxicity-related symptoms, performance status, and quality of life.
- Clear instructions that information entered into STAR will only be reviewed by MSKCC personnel at the time of scheduled outpatient clinic visits, and not in real-time. There will be no formal monitoring of information entered into STAR between clinic visits, and there is no rapid response or automated warning system included in STAR. Patients will be instructed to contact their health care provider(s) by telephone in cases of severe symptoms/toxicities that arise between appointments.
- A telephone number for technical assistance.

### 4.2.4 Clinician Training

Standardized training for participating MSKCC staff (physicians, nurses, session assistants) will be instituted prior to initiation of this protocol. In addition, a study investigator will be available during clinic visits to answer questions of staff, and to remind them of training points. Initial staff training will include:

- Showing staff how to access and login to the STAR administrative site using computers located in clinic.
- Explaining logoff procedures in order to assure the privacy of PHI.
- Demonstrating how to view and print STAR Reports for participating patients, for use during clinic visits.
- Explaining to clinicians how to interpret STAR Reports.
- Clarifying with session assistants that printing STAR Reports for inclusion with other visit materials is a mandatory part of this protocol, and must be done each time a participating patient has an appointment.
- Clarifying with session assistants that each time a participating patient visits clinic, he or she should be encouraged to use STAR on a waiting area computer.
- Encouraging clinicians to discuss the results of STAR reports with patients during visits.

### 4.2.5 STAR Security:

The current design for the STAR system architecture is reproduced in a diagram in Appendix 7. This configuration has been developed with computer security/privacy experts in the MSKCC Information Systems office and is designed to assure that STAR conforms with current MSKCC and HIPAA standards for the protection of patient health information. Patients located outside the MSKCC external firewall will enter data that will be stored on a database server located inside the internal firewall (Appendix 7). The STAR application server will be housed in a DMZ between the internal and external firewalls, and no patient data will be stored on this server. A Security Evaluation Peer Working Group (SEPWG) form has been submitted to the MSKCC Information Security Department outlining the configuration and functionality of the STAR system.

### 4.2.6 Logging into STAR:

The patients with home Internet access may be assigned to login to STAR at home and/or using MSKCC waiting-area computers at the time of outpatient clinic visits. The patients without home Internet access may be assigned to login to STAR using MSKCC waiting-area computers at the time of outpatient clinic visits only.

Each time a patient logs in to the STAR website, he or she will respond to items in the questionnaire, and these responses will be recorded in the STAR database or in the MSKCC Clinical Research Database (CRDB), using technology already developed and commonly used to link MSKCC study questionnaires to the CRDB. Subjects in Group-1 will be able to login to STAR from any Internet-accessible computer on a daily basis, or whenever they wish to record symptoms. In addition, at the time of each outpatient clinic visit to MSKCC, these subjects will be able to login to STAR and enter symptom information using a computer located in the patient waiting-area. Subjects in Group-2 will only be able to login to STAR and enter information at the time of clinic visits, and will not have home access.

The STAR website homepage will include hyperlinks to ASCO patient information about the specific toxicities in the questionnaire (Appendix 1). This content is housed on the ASCO "People Living With Cancer" website (http://www.peoplelivingwithcancer.org), and is derived from the ASCO professional publication *Optimizing Cancer Care: The Importance of Symptom Management* (Kendall/Hunt Publishing Co., 2001). A disclaimer will be included in STAR noting that MSKCC does not control or endorse the information on the ASCO website.

Each time an enrolled patient visits the outpatient clinic, he or she will be verbally reminded by a study Investigator or session assistant that she may login to STAR using computers in a private section of the waiting area. The relevant computer will have the STAR system installed and "bookmarked" for convenience. Technical assistance accessing the system will be available in clinic. Patients will not be offered any financial incentives to login. Patients and/or their caregivers may enter data into STAR, but clinical staff or Investigators will not be permitted to do so on patients' behalf (although they may provide technical assistance).

### 4.2.7 Generation of STAR Reports at Outpatient Visits:

Based on information entered into STAR and recorded in the STAR database, it will be possible to generate summary "STAR Reports" which track symptom trends over time for each patient who is assigned to use STAR, in list or graphic form.

At the time of each such enrolled patient's clinic visits during the study period, summary STAR Reports will be printed by clinic session assistants or an RSA and added to other materials that are routinely reviewed by the nurse and/or medical oncologist as a part of standard care (such as laboratory test printouts, radiology results, chemotherapy records, or past clinic visit dictations). The Report printout will be the second page of these materials, immediately beneath the "Medical Oncology Visit Sheet" which lists patient vital signs and requires a clinician signature.

The technical functionality of STAR will be designed such that information entered by patients using waiting area computers just prior to clinic visits will be available immediately for printing in STAR Reports (and thus for clinician review during that visit). Printing capabilities in the clinician work areas are readily available.

### 4.2.8 Randomization analysis (gynecologic, gastrointestinal, lung and prostate clinics):

**Overview**: In the MSKCC lung, prostate, gastrointestinal and gynecologic medical oncology clinics, a cohort of patients will be randomly assigned to receive various levels of STAR access (clinic plus home access vs. no access). Specifically, patients with prior web/email experience will be randomized to STAR access at clinic visits plus via their home computer(s), or to no STAR access (standard care). Patients without prior web/email experience will be randomized either to receive STAR access at clinic visits, or to no STAR access (standard care).

**Justification**: Even if STAR is shown to be feasible by demonstrating that a group of patients is able and willing to regularly self-report symptoms (Objective 2.1), the question will remain whether this intervention impacts on measures of patient care (Objective 2.2b). We hypothesize that systems like STAR may improve the patient experience of care (for example, as measured by QoL and satisfaction measures), and may enhance clinician awareness of patient symptoms (for example, as measured by the number of calls between nurses and patients, or discussions based around printed STAR reports). A schema in which patients are randomly assigned to receive various levels of STAR access is the optimal design with which to explore associations between STAR use and these measures.

In addition, wide implementation of systems like STAR can represent considerable expense and complicated logistics (training, expert personnel, maintenance, equipment, monitoring of reports). Towards determining the ideal STAR configuration (clinic-only STAR access vs. no STAR access) while minimizing costs, this investigation will allow us to compare configurations in terms of these outcomes.

**Design**: As shown in Figure 3a, patients with prior web/email experience (as established in a baseline questionnaire, Appendix 2) will be randomized to receive STAR access at clinic visits plus from their home computer, or to no STAR access (standard care). Based on a prior paper questionnaire, we anticipate that this will represent at least 60% of the total sample. Individuals in the home-use group will receive email reminders to login at least once weekly, although logging in will not be mandatory. Any grade 3 or 4 toxicities reported from home will trigger an email alert as described in Section 14.1.

Patients without prior web/email experience will be randomized either to receive STAR access at clinic visits, or no STAR access (standard care). This design will

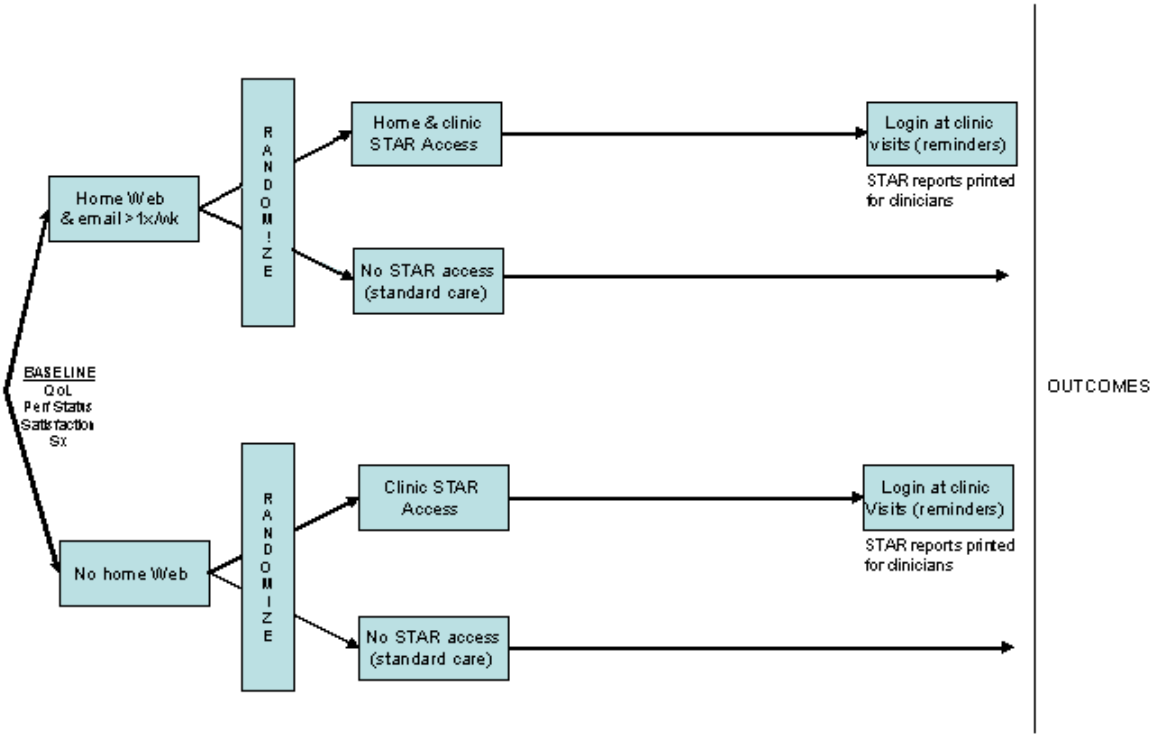
allow us to explore if there is any added value of clinic-based self reporting in a non-technologically avid group.

We do not anticipate blinding of clinicians to patient group assignment. Blinding is not technically feasible given the nature of the STAR system, in which printed Reports are given to clinicians at appointments which show the dates of symptoms as well as the dates of clinic visits. It is readily apparent in these Reports which patients use STAR only at clinic appointments, from home between appointments, or not at all.

Randomization of enrollees will be conducted by the PPA at the time of patient registration as described in Section 12.1.7, and we will obtain the group assignment from the PPA via the CRDB, or over the telephone at the time of enrollment. Specifically:

- Patients who have access to the web and email at home ("Home Web") will be randomized either to the "Home & Clinic STAR Access" group or to the "No STAR Access" group.
- Patients without home web/email access ("No Home Web") will be randomized either to the "Clinic STAR Access" group or the "No STAR Access" group.

**Figure 3a**. Randomization schema



**Measured outcomes**: The outcomes compared between groups in this analysis will be mean change in QoL as measured by the EuroQoL EQ-5D instrument (Appendix 2), and change in patient satisfaction based on measures developed by the Picker Institute (Appendix 6) (69). In addition, we will explore differences in the number of telephone calls between nurses and patients (logged in MSKCC clinics as a part of routine care), and number of dose reductions (accessible in the electronic medical record).

**Sample size**: Based on prior paper surveys in this patient population, we anticipate a mean baseline QoL score of 70%. A 20% improvement in mean QoL score due to STAR would be considered clinically significant (ie, a change from 70% to 90%). With a sample including 75 patients per arm, a 20% difference in mean QoL scores between groups (70% vs. 90%) could be detected with an alpha of 0.05 and 80% power.

**Interpretation**: If QoL or satisfaction significantly improves with STAR, this will suggest that patient self-reporting may provide benefits to patient care, meriting further investigation to determine if improvements result from the mere process of self-reporting, or due to clinical actions (for example, resulting from augmented communication with treating clinicians). However, if these measures are not superior in the presence of STAR but the approach is found to be feasible, other potential values of STAR may merit investigation (for example, improved efficiency or comparability to clinician reporting).

### 4.3 Baseline Information Questionnaire (all clinics):

Mediating variables that we expect may affect levels of STAR utilization include age, level of education, employment status, prior Internet experience, and baseline quality of life. Therefore, these will be measured at baseline via a paper patient questionnaire (Appendix 2). This questionnaire will be administered by the consenting professional immediately after obtaining Informed Consent and Research Authorization. Additional baseline information, including cancer type, stage of disease, current/planned therapy, and baseline performance status, will be obtained by using the MSKCC electronic medical record.

### 4.4 Outcomes (all clinics):

**Feasibility analysis (gynecologic oncology clinic)**: The primary outcome of this study is patient willingness to use STAR, based on utilization as described in Section 9.1. Patient assessment of the usefulness of STAR is a secondary outcome, and will be assessed via interim and exit questionnaires administered to subjects during the study and at the time of study completion or disenrollment (Appendix 6), as described in Section 9.2.1. In addition, clinician perception of the potential value of STAR is a secondary outcome. This will be evaluated via an email survey and/or questions asked at a scheduled team meeting including

physicians, nurses, and session assistants who cared for enrolled patients (Appendix 5), as described in Section 9.2.2.

**Randomization analysis (lung, prostate, gastrointestinal and gynecologic medical oncology clinics)**: In addition to the above feasibility measures, the impact of STAR use on patient QoL and satisfaction will be assessed as described in Section 4.2.8.

## 5.0 CRITERIA FOR SUBJECT ELIGIBILITY

### 5.1 Subject Inclusion Criteria:

- Age >18 years.
- Diagnosis of gynecologic (ovarian; cervical; uterine; primary peritoneal), lung (non-small cell; small cell), gastrointestinal (colorectal, rectal, gastric, esophageal, GI neuroendocrine, small intestine malignancy, pancreatic, hepatocellular) or prostate malignancy.
- Receiving primary medical oncology care at MSKCC medical oncology outpatient clinics.
- Starting a new cytotoxic chemotherapy regimen at the time of enrollment not on a clinical trial (or a new hormonal therapy in the case of prostate cancer patients only), with treatment expected to continue for at least four weeks from the time of enrollment.
- Signed informed consent and Research Authorization.

### 5.2 Subject Exclusion Criteria:

- ECOG performance status greater than 2.
- Unable to read and comprehend English language text.

## 6.0 RECRUITMENT PLAN

Patients will be recruited through the outpatient clinics of the Solid Tumor Division at MSKCC. During the enrollment period, on selected days that cancer patients are seen in the selected MSKCC medical oncology outpatient clinics, a list of all patients will be generated ahead of time as the potential pool of enrollees, using the MSKCC computerized scheduling system. Patients on this list will be approached on clinic appointment days, either in the waiting-area or in the examining room area in order to assess eligibility, explain the protocol, and offer enrollment. Patients who are eligible and agree to participate in the study will be required to sign a statement of Informed Consent and Research Authorization form, as described in Section 15.0.

Because patients will be invited to participate in the research protocol based on having a diagnosis of a gynecologic, gastrointestinal, lung, or prostate malignancy and initiation of

a new antineoplastic regimen, as determined from clinic visit lists, a Limited Waiver of Authorization for Recruitment Purposes will be required to identify potential subjects for protocol enrollment. Subjects who ultimately do enroll will sign a Research Authorization (Appendix 3) but the Limited Waiver of Authorization for Recruitment Purposes is requested to cover review of records necessary for pre-enrollment identification of potential research subjects. This activity is described in the MSKCC Limited Research Authorization syntax as follows: Investigators "may screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

"During the initial conversation between the Investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The Investigator/research staff may also review portions of their medical records at MSKCC in order further to assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

"In most cases, the initial contact with the prospective subject will be conducted either by the study team, Investigator or the research staff working in consultation with the study team. The recruitment process we have outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal personally identifiable health information (PHI) will be maintained as part of a screening log. For these reasons, we seek a limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable)."

For those patients in the randomization cohort (enrollees in gynecologic, gastrointestinal, prostate or lung cancer patients), we will obtain a group assignment from the PPA, as described in Section 12.1.7.

## 7.0 ASSESSMENT/EVALUATION PLAN

**Feasibility cohort (gynecologic oncology clinic)**: First we will assess use of the STAR system itself, as measured by the number of times subjects login (described in Section 9.2). Second, we will evaluate patient impressions of the usefulness of STAR via a paper interim/exit-questionnaire reproduced in Appendix 6 (described in Section 9.2.1). Third, we will elicit clinician perceptions of the potential value of STAR in a scheduled team meeting, based on questions itemized in Appendix 5 (described in Section 9.2.2).

**Randomization cohort (lung, prostate, gastrointestinal and gynecologic medical oncology clinics)**: We will assess the potential impact of STAR on patient QoL and satisfaction (Section 4.2.8)

## 8.0 TOXICITIES/SIDE EFFECTS

- Not applicable.

## 9.0 OUTCOMES

### 9.1 Primary Outcome:

The primary objective of this study is to evaluate patients' willingness to use an Internet-based system to track their own symptoms and quality of life during chemotherapy treatment. In this pilot, we will measure several parameters related to patients' utilization of the STAR system in four different cancer-type patient cohorts, in order to evaluate the potential for implementation of collecting patient self-reported measures in oncology practice. To gauge patients' willingness to record their experiences we will first record the ratio of the number of patients approached for study participation to the number who enroll. Second, we will evaluate the extent to which patients who enroll in the protocol actually use the STAR system. We will accomplish this by measuring how often each user accesses the STAR system, when utilization occurs in relation to chemotherapy administration, and the sites of use (home versus clinic).

For each patient, we will define a minimum study period (interval) of 8 weeks beginning on the day of initiating a new chemotherapy regimen subsequent to enrollment, and lasting for an observation period of up to one year.

Within each of the four cancer type cohorts, we will consider two groups of patients for these descriptive analyses: those with and without home Internet access. As a crude measure of feasibility, we will consider the study results to suggest that STAR is a strategy warranting larger scale evaluation if half of home Internet users log into STAR at least once during the study period and if one-third of patients without home Internet access login to STAR at least once. In our analysis, we will look at STAR utilization (1) over time; (2) in terms of number of clinic visits per individual; and (3) by number of cycles of chemotherapy received.

Based on the results of this pilot study, we will plan to pursue further research of STAR in a controlled trial setting to assess if it improves patient satisfaction with care; improves the recording of patient symptoms, performance status, and quality of life during routine cancer care with chemotherapy; and if it improves the collection of toxicity information (symptom AEs).

Mediating variables that we expect may affect levels of utilization include cancer type diagnosis, age, level of education, prior Internet experience, and baseline ECOG

score/quality of life. Therefore, these will be measured at baseline via a questionnaire (Appendix 2).

## 9.2 Secondary Outcomes:

### 9.2.1 Patient Assessment of STAR:

Patient assessment of the usefulness of STAR will be measured via an interim/exit questionnaire (Appendix 6). Items in this questionnaire are adapted from validated measures used in prior studies evaluating satisfaction with information technology interventions (63-68) and instruments developed by the Picker Institute (69), and makes use of an ordinal scale for recording responses. Questions address two specific areas: ease of use (ease of login, ease of data entry, understandability of questions), and perceived usefulness (memory triggering, use of information by doctors/nurses, feeling of control over own care, feeling that care was improved).

### 9.2.2 Clinician Assessment of STAR:

At the completion of the study period, an email clinician survey will be administered, and a team meeting will be scheduled with all clinicians and support personnel involved in the care of enrolled patients (physicians, nurses, Session Assistants). Specific open-ended questions will be asked verbally to assess qualitative impressions of STAR, and to obtain suggestions for future development of STAR (Appendix 5). Questions will include whether STAR was felt to be useful overall, not useful, or detrimental; whether it saved or consumed time; whether summary reports should be used to replace other assessment documents in the patient chart; and whether clinicians feel that patient self-generated reports accurately depict levels of toxicity.

Clinician dictations for enrolled patients will be reviewed to assess if information from database-generated STAR Reports was included.

### 9.2.3 Comparison of Patient and Clinician Toxicity Assessments:

Patients enrolled in this pilot will not also be in a clinical treatment trial, and therefore there will not be routine collection of research-grade toxicity information by clinicians/RSAs. As a result, there will not be a consistent and reliable source of clinician-collected data for comparison to patient reports entered into STAR. However, in order to gain preliminary insights into this issue, at the completion of this pilot, we will conduct a chart review of enrolled patients. For those individuals for whom toxicity data were recorded via optically scanned patient Visit Sheets, we will compare results with those entered by patients into STAR.

### 9.2.4 Content Hyperlinking:

Frequency of patient hyperlinking to ASCO online symptom information from the STAR frontpage will be tracked automatically by the STAR database. This information will be used to assess the degree to which enrollees wished to view symptom-related content. It is standard practice for disease-based websites to offer informational content.

### 9.2.5 Impact on the Patient Experience of Care (Gynecologic, Gastrointestinal, Lung and Prostate):

In addition to the above measures, outcomes compared between groups will include mean change in QoL as measured by the EuroQoL EQ-5D instrument (Appendix 2), and change in patient satisfaction based on measures developed by the Picker Institute (Appendix 6) (69). In addition, we will explore differences in the number of telephone calls between nurses and patients (logged in MSKCC clinics as a part of routine care), and number of dose reductions (accessible in the electronic medical record).

## 10.0 CRITERIA FOR REMOVAL FROM STUDY

### 10.1 Withdrawal from Study:

- Patients may voluntarily withdraw from the study at any time for any reason. The Investigator also may withdraw patients from the study. As an excessive rate of withdrawals can render the study uninterpretable, efforts will be made to avoid unnecessary withdrawals. The reason(s) for withdrawal will be recorded.

### 10.2 Censoring and Inevaluable Patients:

- Efforts shall be made to account for all patients entered into the study during the evaluation period. Patients who die during the study, enter hospice

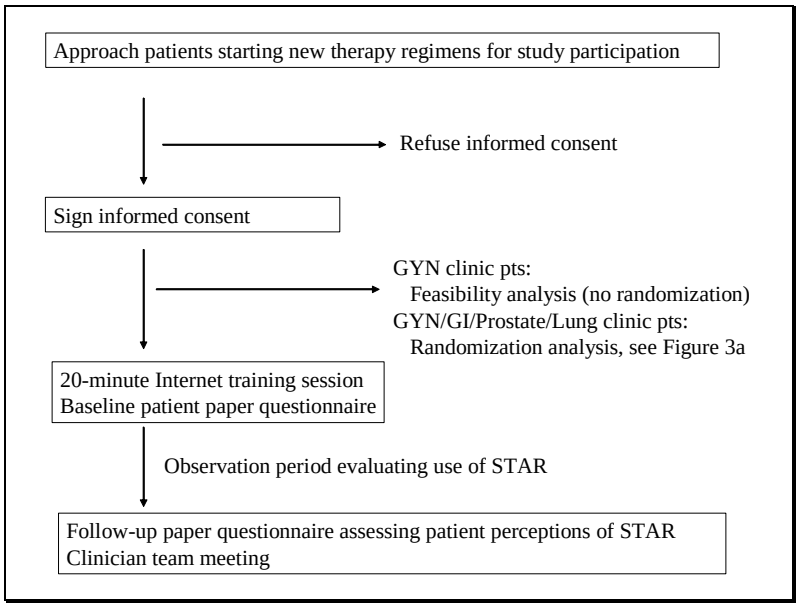
programs, or are lost to follow-up will be described in the summary analysis and will not be censored. However, we anticipate that no patients will be lost to follow-up, based on high baseline rates of patient follow-up in MSKCC outpatient clinics.

## 11.0 BIOSTATISTICS

### 11.1 Accrual:

In the gynecologic oncology clinic, an accrual period will continue until at least 80 patients are enrolled, with at least 25% without home Internet access (Figure 3b. This proportion is similar to patterns of Internet home access observed in prior surveys of MSKCC outpatients (Section 3.4). Based on average clinic census and experience administering questionnaires in this patient population, we anticipate that accrual will be complete within 12 weeks. For patients in the prostate and lung cancer clinics, accrual will continue until approximately 150 patients with prior web/email experience and 150 patients without prior web/email experience are enrolled (detailed in Section 4.2.8).

**Figure 3b: Patient Enrollment Schema**




We will initially accrue patients only in the gynecologic oncology clinic, and will use the scroll-down version of the online questionnaire (Appendix 1, IIa). Based on user feedback, we may alter the aesthetics of the interface to address patient feedback prior to opening accrual in the prostate and lung clinics. Any differences in the interface between clinics will be acknowledged in the data analysis (Section 11.2).

### 11.2 Primary Objective:

For patients in all clinics (gynecologic, gastrointestinal, lung, and prostate cancer), the primary objective of this study is to measure patient willingness to use STAR in each of four cancer types. For each cohort and overall, we will calculate summary statistics for several measures of utilization, including how often each user accesses the STAR system, when utilization occurs in relation to administration, and the sites of use (home versus clinic). Two groups of patients will be considered in these descriptive analyses: those with and without home Internet access. As a crude measure of feasibility, we will consider the study results to suggest that STAR is a strategy warranting larger scale evaluation if half of home Internet users log into STAR at least once during the study period and if one-third of patients without home Internet access login to STAR at least once. In our analysis, we will look at STAR utilization (1) over time; (2) in terms of number of clinic visits per individual; and (3) by number of cycles of chemotherapy received. We will analyze results across and within each of the four cancer type cohorts.

Because this is a pilot study and by nature exploratory, it is not clear which of these endpoints will yield informative data towards future study. Patients who do not experience significant toxicity or functional status impairment during chemotherapy may choose not to use STAR, nor may patients experiencing the most severe toxicity symptoms. As a result, response rates may appear lower than they would be if STAR were to be implemented for all patients as a part of routine care.

In addition to calculating the proportion of STAR users compared to the total number of enrollees (users:enrollees), we will also calculate the proportion of users compared to the total number of patients approached (users:approached), including those who refused enrollment or Informed Consent. We project that two-thirds of approached patients will agree to be enrolled, sign Informed Consent/Research Authorization, and complete computer training for the STAR system (Figure 3).

During the study interim and exit interviews, questions will specifically address reasons why STAR was not used (Appendix 6). For example, we will distinguish between technical obstacles to use, non-use related to absence of symptoms, and limited use related to severity of symptoms. We anticipate that STAR will be utilized less frequently by patients at both ends of the spectrum: those lacking and with the worst symptoms.

We will acknowledge in the analysis if the interface is altered aesthetically following implementation in the gynecologic oncology clinic, but prior to implementation in the prostate, gastrointestinal, or thoracic oncology clinics. As noted in Section 4.0, the intention of any changes would be to improve readability and navigation of the online questionnaire, based on patient feedback.

### 11.3 Secondary Outcomes for Patients:

In the feasibility cohort (gynecologic oncology clinic), as a secondary outcome, patient assessment of the usefulness of STAR will be assessed via a questionnaire administered to subjects at the time of study completion or disenrollment (Appendix 6). Items in this

questionnaire are adapted from validated measures used in prior studies of satisfaction with information technology interventions (63-68) and instruments developed by the Picker Institute (69), and makes use of an ordinal scale for recording responses. Summary statistics will be calculated for each item in the questionnaire. Patients will be asked if STAR Report information was used as a starting point for discussions during clinic visits.

In the randomization cohort, if QoL or satisfaction measures significantly improve by 20% with STAR (Section 4.2.8), this will suggest that patient self-reporting may provide benefits to patient care, meriting further investigation to determine if improvements result from the mere process of self-reporting, or due to clinical actions (for example, resulting from augmented communication with treating clinicians). However, if these measures are not superior in the presence of STAR but the approach is found to be feasible, other potential values of STAR may merit investigation (for example, improved efficiency or comparability to clinician reporting).

### 11.4 Secondary Outcomes for Clinicians:

Clinician qualitative impressions of STAR will be gathered at the end of the study via a paper survey and during a team meeting, at which open-ended questions will be asked (Appendix 5). These will be reported in summary form, and will be principally used towards future development of STAR. Clinicians will be asked if STAR Report information was used as a starting point for discussions during clinic visits.

Clinician impressions of STAR are of interest because they may influence how STAR or a similar system is used clinically. The purpose of this survey and group meeting is to obtain feedback regarding how the STAR system impacted on clinician workflow. Physicians and RNs will be asked for specific suggestions regarding how the system could be altered and whether it is perceived as potentially valuable, neutral, or a hindrance to the provision of patient care.

### 11.5 Missing Data:

Summary statistics will be tabulated for each of the three domains evaluated by STAR (CTCAE toxicity symptoms, ECOG performance status, EuroQOL 5-D quality of life assessment). For each patient who accessed STAR during the study period, the number of completed question sets for each domain will be measured. This will provide insight as to whether patients exhibit preferences towards some information categories over others.

### 11.6 Hyperlinks:

Frequency of patient hyperlinking to ASCO online symptom information from the STAR frontpage will be tracked automatically by the STAR system. This information will be used to assess the degree to which enrollees wished to view symptom-related content. It is standard practice for disease-based websites to offer informational content.

## 12.0 SUBJECT REGISTRATION PROCEDURES

### 12.1 Subject Registration:

**12.1.1.** The following persons can obtain informed consent:

Ethan Basch, MD; Dorothy Dulko, NP; Paul Sabbatini, MD; Martee Hensley, MD; Deborah Schrag, MD; Mary McCabe, RN; Mark Kris, MD; Vincent Miller, MD; Naiyer Rizvi, MD; Lee Krug, MD; Christopher G. Azzoli, MD; Jorge Gomez, MD; Howard Scher, MD; Susan Slovin, MD; David Solit, MD; Lewis Kampel, MD; Michael Morris, MD; Breda Moynagh, RN; Mary-Ellen Fogarty, RN; Gabrielle Arauz, RN; Amparo Camacho, RN; Anne Capozzi, RN; Chris Liebertz, RN, NP; Ellen Dermody, RN; Anthony DeLaCruz, RN; Tracy Curley, RN; Nancy Houlihan, RN; Ann Culkin, RN; Anne Haughney, RN; Maureen Bland, RN; Denise O'Rourke, RN; Kim Plastini, RN; Leslie Tyson, RN; Barbara Pizzo, RN; Megan Dunne, RN; Amy Farmer, RN, NP; Diane Paolilli, RN; Charles Tilley, RN; Catherine Custodio, RN; Patty Albanese, RN; Jennifer Olstrom, RN; Jeanine Gordon, RN; Mary Theresa Hanna, RN; Bernadette Giaccone, RN; William Pao, MD; Denise O'Rourke, RN.

**12.1.2.** Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

**12.1.3.** Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

**12.1.4.** Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

**12.1.5.** All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

**12.1.6.** During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual [Last, First Name]
Notice of Privacy Status [Yes, No, N/A]

Research Authorization [Date]
MSKCC IRB Protocol#
Attending of Record (if applicable) [Last, First Name]

Consenting Professional [Last, First Name]
Informed Consent Date
Patient's Full Name [Last, First Name]
Patient MRN

**12.1.7. Randomization cohort (enrollees in gynecologic, gastrointestinal, lung and prostate cancer clinics)**: For those enrollees in the MSKCC gynecologic, gastrointestinal, lung and prostate cancer clinics (the "randomization cohort," described in Section 4.2.8 and shown in Figure 3a), a group assignment will be randomly assigned by the PPA at the time of patient registration.

- Patients who have access to the Web and email at home ("Home Web") will be randomized either to the "Home & Clinic STAR Access" group or to the "No STAR Access" group.
- Patients without home web/email access ("No Home Web") will be randomized either to the "Clinic STAR Access" group or the "No STAR Access" group.

We will obtain each patient's assignment from the PPA via the CRDB, or over the telephone at the time of enrollment.

## 13.0 DATA MANAGEMENT ISSUES

### 13.1 Personnel:

The study Investigators Ethan Basch, MD and Dorothy Dulko, NP will be responsible for activities related to project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. The data collected for this study will be entered into a secure database (Clinical Research Database, CRDB). Source documentation will be available to support the computerized patient record.

A computer Network Administrator will serve as a member of the research team, and will work in collaboration with study Investigators John Speakman, Kai-Hsiung Lin, and David Artz, MD of MSKCC Information Systems. The Network Administrator will be responsible to maintain the function of the server, electronic security, technical support, and website functionality throughout the study.

### 13.2 Web Security:

Three of this study's Investigators are information technology experts at MSKCC (John Speakman, Kai-Hsiung Lin, David Artz, MD). All of these individuals are experienced with issues of electronic security, such as security of the MSKCC Clinical Research Database (CRDB) and the Intranet-based electronic medical record. All technology

design and functionality will be built and reviewed with direct input of these Investigators.

This study will involve the collection of confidential patient self-reports of toxicity data and functional status over the Internet. Encryption technology will be used to assure security. Patient data collected by this system will be stored on a secure MSKCC server behind the MSKCC firewall and/or in the MSKCC Clinical Research Database (CRDB). Access to data will be password protected, and only individual patients, appropriate clinical staff, and research study staff will have access to passwords. Data will only be reviewed by staff when directly related to patient care or conduct of this study. Patients will only be able to view their own Reports on computers outside of the firewall if reasonable security precautions can be assured.

### 13.3 Quality Assurance:

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team weekly.

## 14.0 PROTECTION OF HUMAN SUBJECTS

### 14.1 Rapid Reporting of Potentially Serious Toxicities:

Patients will be informed at multiple time points that STAR is not a rapid response system, is not a replacement for contacting a physician's office for serious health concerns (such as severe toxicity-related symptoms), and that there is no regular formal monitoring of information entered into STAR. This will be printed in the Informed Consent (Appendix 3), told verbally to enrollees at the time of accrual, and will be included on a screen (browser page) in STAR every time a patient logs in (Appendix 1). In addition, anytime a patient enters a toxicity grade of 3 or 4 into STAR, a popup box will appear on the screen reminding them to consider calling their physician's office.

Nonetheless, any time an online STAR questionnaire is submitted by a patient which includes a toxicity grade of 3 or 4, an automated email will be generated by STAR and sent to Ethan Basch, MD, the medical oncology fellow who is coordinating this study and a designated clinician in each DMT. They will then contact the primary team (physician and/or nurse) regarding the reported toxicity. In addition, the primary medical oncologist for each enrolled patient will have the option during this study to also receive a copy of the STAR-generated email or to have the email forwarded to a designated clinic nurse, although this will not be a requirement (the primary oncologist for each patient will be identified at the time of enrollment by the consenting investigator). The STAR-generated email will state the following, for example: "*Jane Smith MRN #XXXXXXX*, a patient of

*Dr. Sabbatini*, reported grade 3 nausea, a potentially serious toxicity, into the STAR online system, at 4:47pm on 4/3/04."

### 14.2 Privacy:

This study will involve the collection of confidential patient self-reports of toxicity data and functional status over the Internet. Patient data collected by this system will be stored on a secure MSKCC server behind the MSKCC firewall. Encryption technology will be used to assure security. Patients will only be able to view their own STAR Reports on computers outside of the firewall if reasonable security precautions can be assured. Access to data will be password protected, and only individual patients, appropriate clinical staff, and research study staff will have access to passwords. Data will only be reviewed by staff when directly related to patient care or conduct of this study.

The Research Staff will ensure that protocol patients have received the Notice of Privacy Practice. A Research Authorization form will be completed by the Principal Investigator and approved by the IRB and Privacy Board.

### 14.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

## 15.0 INFORMED CONSENT PROCEDURES

### 15.1 Informed Consent and Research Authorization:

Patients will be required to sign a statement of informed consent which meets the requirements of the code of Federal Regulations (Federal Register Vol. 46, No. 17, Jan. 27, 1981, part 50) and the IRB of this center. A consent form is appended (Appendix 3).

Enrollees will sign a Research Authorization form permitting review of their medical record for the purpose of gathering data for this study, including cancer type, stage of disease, current/planned therapy, baseline performance status, chemotherapy received during the study, and dates of clinic visits, as well as all information entered into STAR (Appendix 3).

### 15.2 Consent Process:

One of the Consenting Professionals will review the rationale for the study procedures with the patient. The discussion will review the potential benefits of this program, the possible risks (for example, the security of entered information) and the procedures being taken to minimize these risks.

### 15.3 Physicians and Health Professionals Eligible to Register Patients:

Informed consent may be obtained by one of the Investigators listed as a Consenting Professional on the protocol facesheet. Any Fellow or Nurse who obtains consent will have the consent co-signed by one of the Attendings designated on the front page of the protocol that is authorized to obtain consent.

### 15.4 Documentation of Informed Consent:

The informed consent will be signed by the patient and consenting professional in triplicate. For registration on the study, a completed copy of the consent form will be faxed to the Clinical Trials Office at MSKCC [FAX number: 212 557-0787]. A signed original copy of the consent form will be given to the patient. The second original will be placed in the medical record, and the third maintained in the Clinical Trials Office.

### 15.5. Procedures for Obtaining Research Authorization:

Before any protocol-specific procedures are carried out, Investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients will sign the Research Authorization component of the informed consent form (Appendix 3). The Research Authorization requires a separate set of signatures from the patient and the research staff consenting the subject. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

## 16.0 APPENDICES

Appendix 1: Example screen shots from STAR system

Appendix 2: Baseline Patient Information Questionnaire

Appendix 3: Informed Consent for Patients / Research Authorization Form

Appendix 4: Symptom Questionnaire for Patients – Paper Version

Appendix 5: Clinician Surveys

Appendix 6: Patient Assessment Interim/Exit Questionnaire

Appendix 7: System Architecture Diagram

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