Patient-Reported Outcomes for Toxicity and Symptom Monitoring in Oncology

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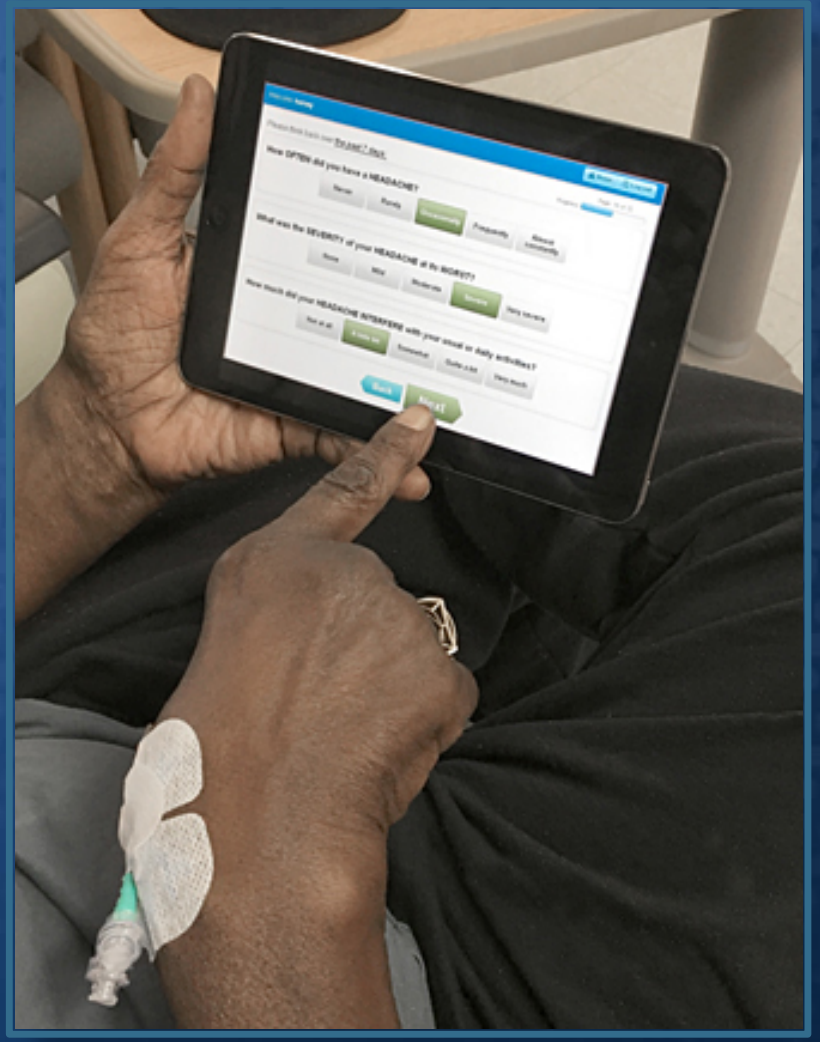
June 22, 2019



Disclosures

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- **Advising**: Sivan; Self Care Catalysts; CareVive; CMS/RTI, Dana-Farber Cancer Institute, Memorial Sloan Kettering
- **Board of Directors**: ASCO

Evolution of Therapies in Oncology

Cytotoxics → Oral Oncolytics → Immumotherapies

- Changing toxicities and dynamics of toxicities
- Importance of monitoring and management of symptoms remains
- Increasing focus on chronic and unexpected serious toxic events

	TAXOTERE 75 mg/m2 every 3 weeks	
ADVERSE REACTION	**ANY (%)**	**GRADE 3/4 (%)**
Anemia	67	5
Neutropenia	41	32
Thrombocytopenia	3	1
Infection	32	6
Epistaxis	6	0
Allergic Reactions	8	1
Neuropathy Sensory	30	2
Neuropathy Motor	7	2
Rash/Desquamation	6	0
Alopecia	65	N/A
Nail Changes	30	0
Nausea	41	3
Diarrhea	32	2
Stomatitis/Pharyngitis	20	1
Taste Disturbance	18	0
Vomiting	17	2
Anorexia	17	1
Cough	12	0
Dyspnea	15	3
Cardiac function	10	0
Fatigue	53	5
Myalgia	15	0
Tearing	10	1
Arthralgia	8	1

Table from Docetaxel U.S. Drug Label

	TAXOTERE 75 mg/m2 every 3 weeks	
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Table from Docetaxel U.S. Drug Label

Standard Approach to Toxicity Monitoring in Oncology

- "Common Terminology Criteria for Adverse Events" (CTCAE)
- Item library, designed for clinicians to complete
- About 800 items total (10% of items are symptom)

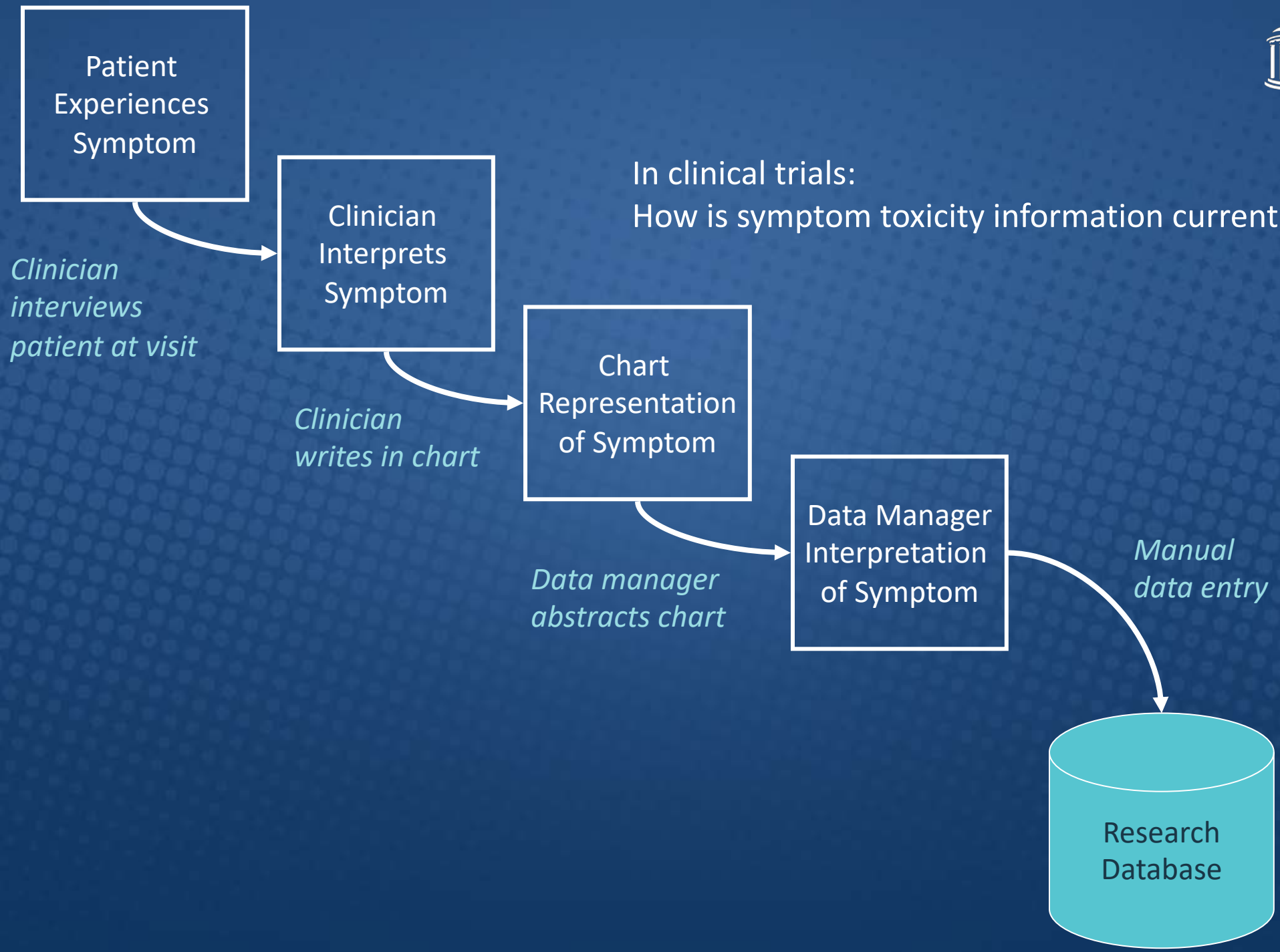
CTCAE/MedDRA Term	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated

Is Clinician Toxicity Symptom Reporting Reliable?

Symptom	ICC	95% CI
Constipation	0.48	0.36; 0.58
Diarrhea	0.58	0.49; 0.66
Dyspnea	0.69	0.62; 0.75
Fatigue	0.50	0.39; 0.59
Nausea	0.52	0.41; 0.60
Neuropathy	0.71	0.65; 0.76
Vomiting	0.46	0.34; 0.56

Atkinson/Basch: Qual Life Res, 2011

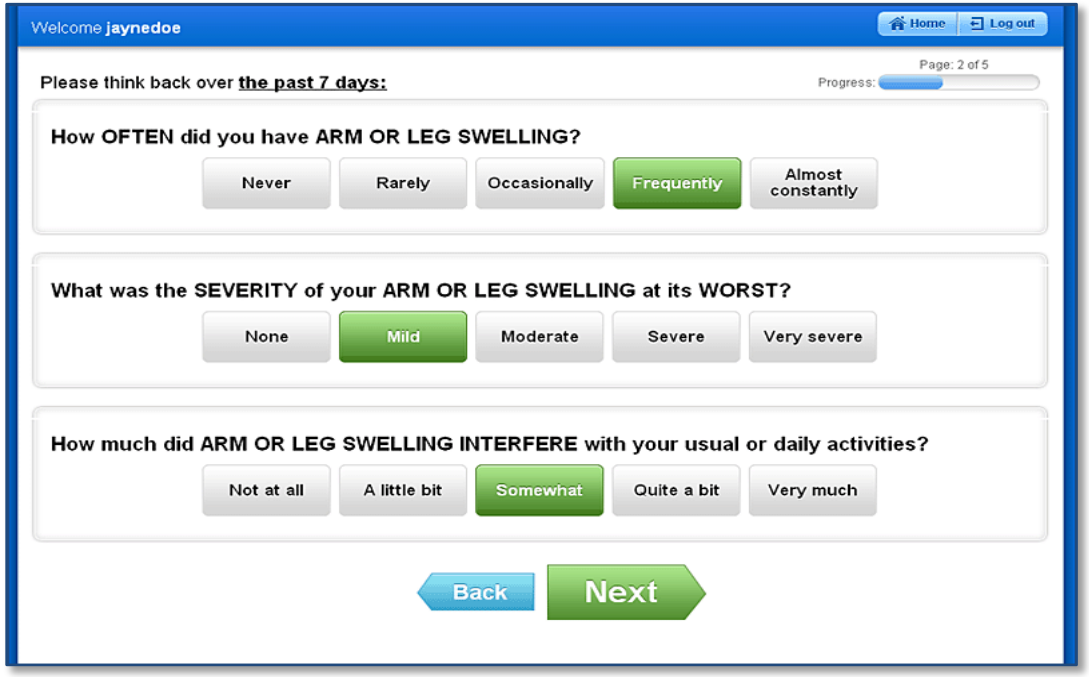
In clinical trials:
How is symptom toxicity information currently collected?



Patient Experiences Symptom

Alternative approach

Patient direct reporting of symptoms



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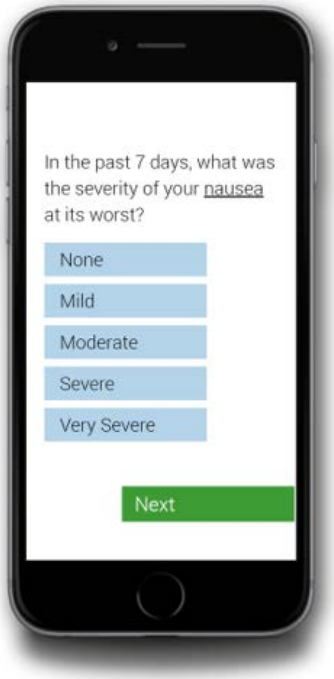
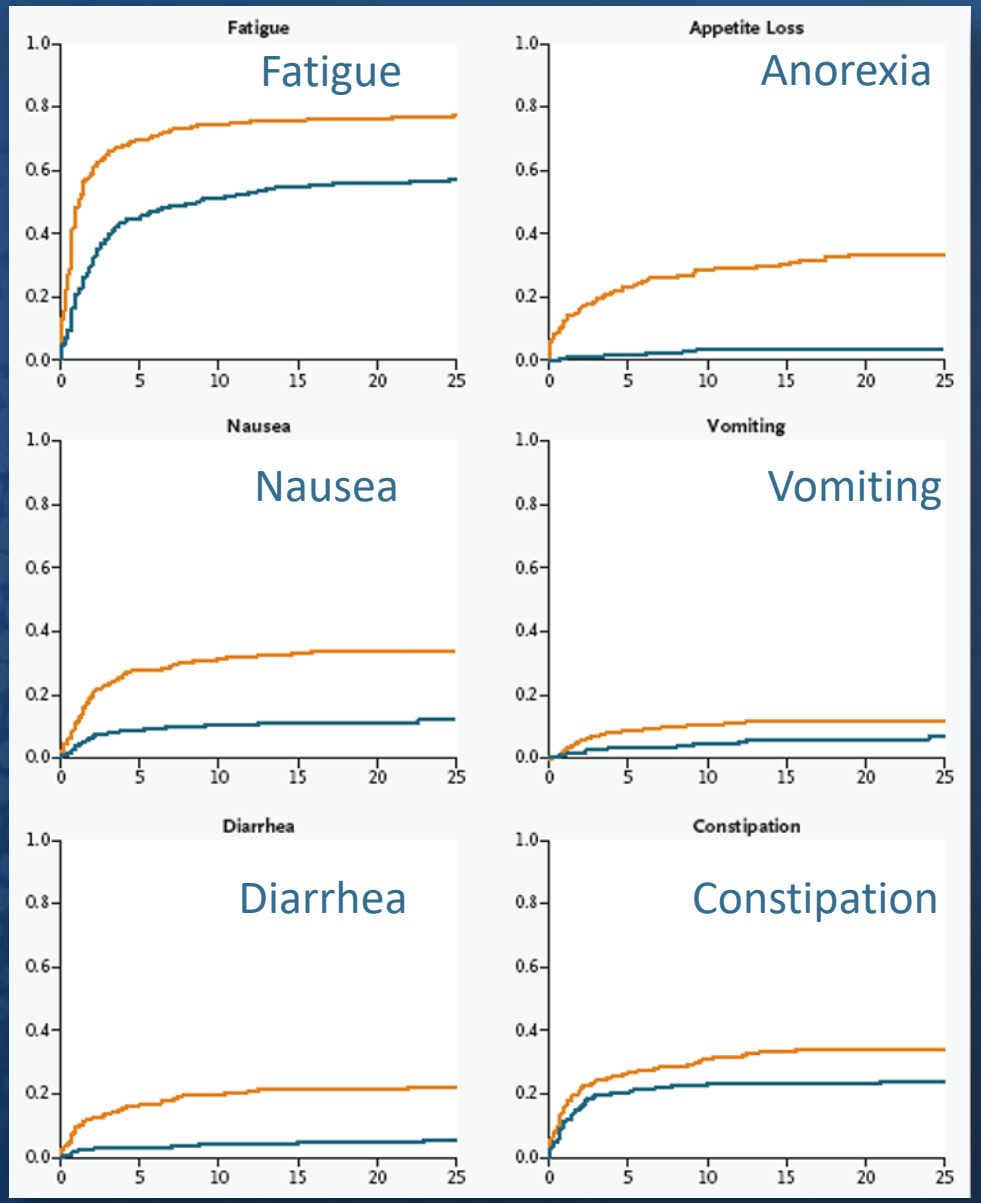


Mobile

Automated Telephone Systems

How Does Patient and Clinician Reporting Compare?



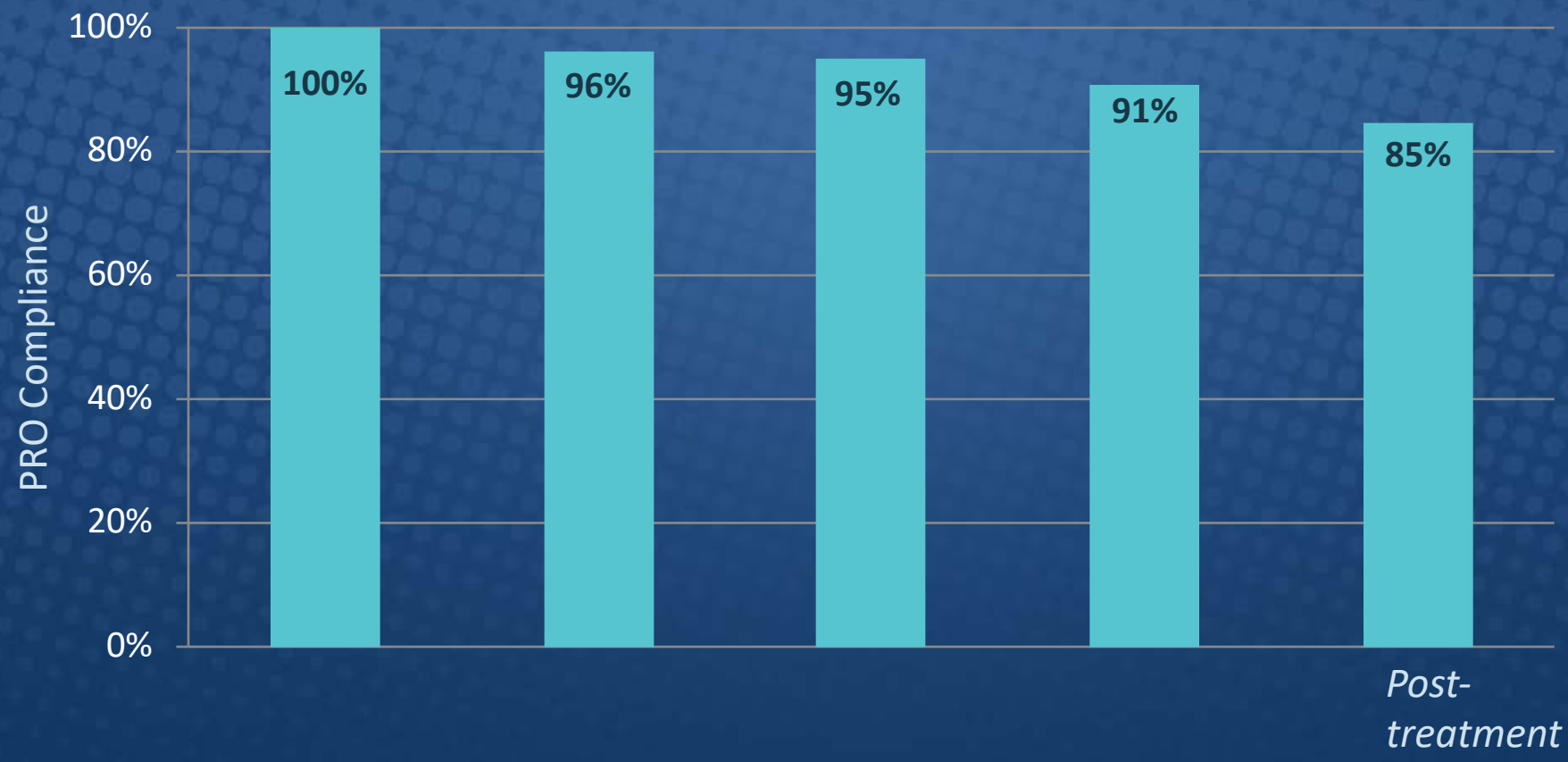
Patient-reported

Clinician-reported

Basch: NEJM, 2010

Is Patient Toxicity Reporting Feasible in Trials?

- In 9 U.S. multicenter trials (CALGB #70501)



Basch et al: JAMA Oncology, 2017

Sharing PROs with Clinicians

For half of patients, reports NOT shared with clinicians

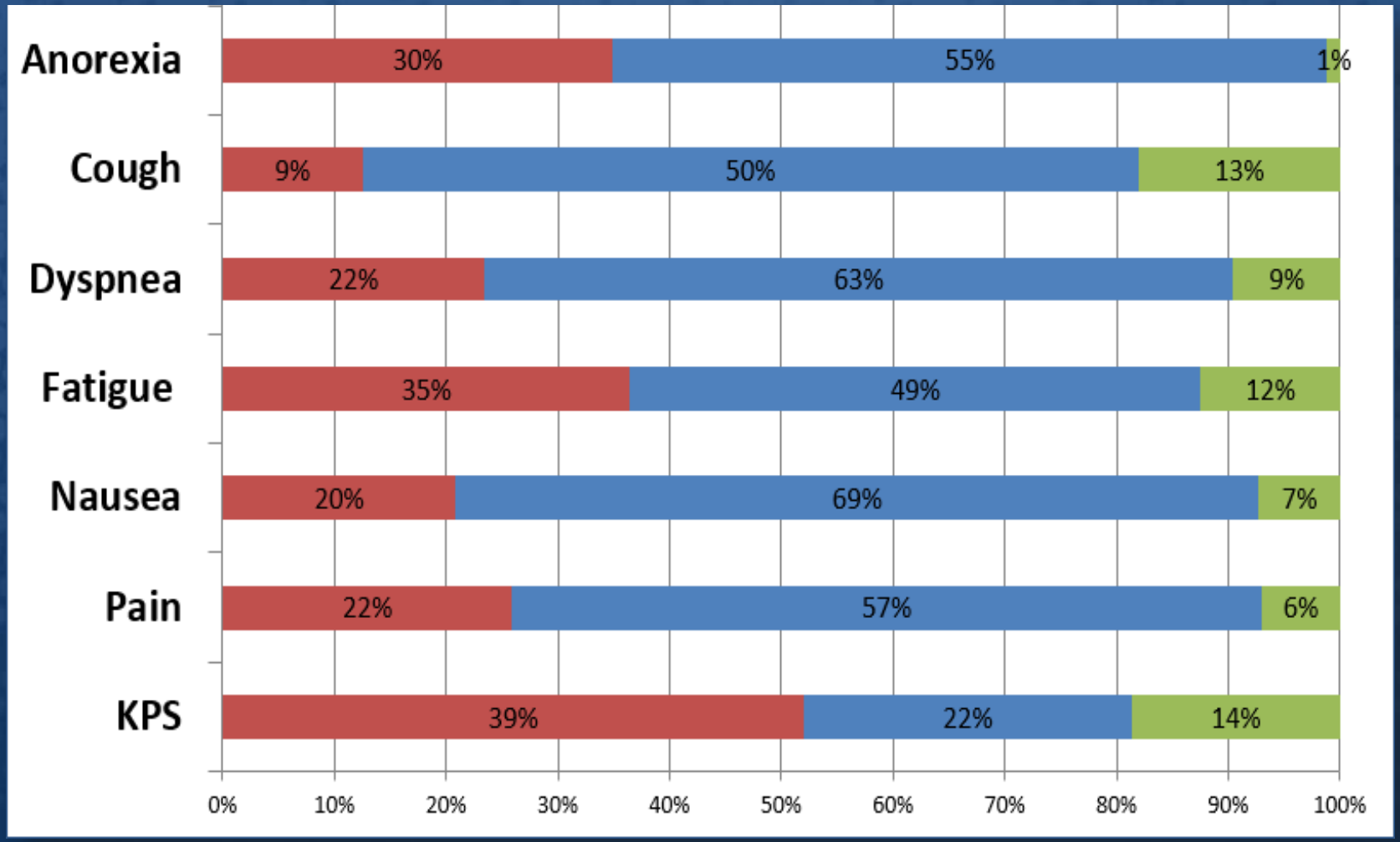
For the other half of patients, clinicians saw this:

Adverse symptom	Patient self report	Date	Agree?	Clinician reassign	Attribution
ALOPECIA	GRADE 0	6/15/2011 10:54 AM	Agree	GRADE 0	N/A
ANOREXIA	GRADE 1	6/15/2011 10:53 AM	Disagree	GRADE 2	Unrelated
COUGH	GRADE 1	6/15/2011 10:53 AM	Agree	GRADE 1	N/A
DYSPNEA	GRADE 1	6/15/2011 10:51 AM	Disagree	GRADE 2	Unlikely
EPIPHORA	GRADE 0	6/15/2011 10:55 AM	Agree	GRADE 0	N/A
EPISTAXIS	GRADE 0	6/15/2011 10:55 AM	Agree	GRADE 0	N/A
FATIGUE	GRADE 0	6/15/2011 10:51 AM	Disagree	GRADE 1	Possibly
KPS	100%	6/15/2011 10:55 AM	Agree	GRADE 0 / GRADE 1 / GRADE 2 / GRADE 3 / GRADE 4	N/A
MUCOSITIS/STOMATITIS	GRADE 1	6/15/2011 10:54 AM	Agree		N/A
MYALGIA	GRADE 1	6/15/2011 10:51 AM	Agree	GRADE 1	N/A
NAUSEA	GRADE 0	6/15/2011 10:54 AM	Agree	GRADE 0	N/A
PAIN	GRADE 0	6/15/2011 10:51 AM	Agree	GRADE 0	N/A
SENSORY NEUROPATHY	GRADE 1	6/15/2011 10:50 AM	Agree	GRADE 1	N/A
VOICE CHANGES/HOARSENESS	GRADE 1	6/15/2011 10:54 AM	Agree	GRADE 1	N/A

Lock Submit

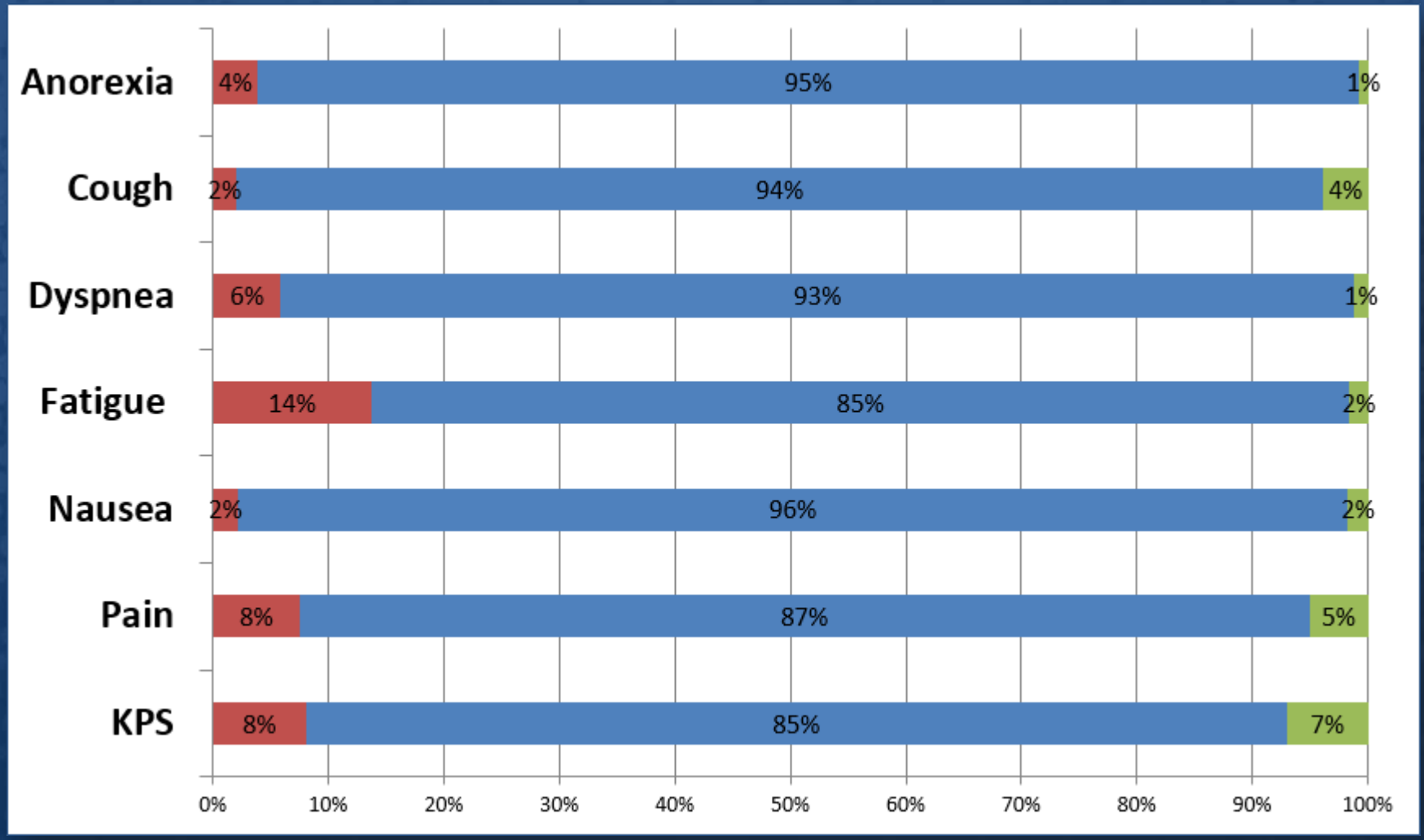
Basch: Clinical Trials, 2015

Investigator-Patient Agreement when PROs NOT Shared



Basch: Clinical Trials, 2015

Investigator-Patient Agreement when PROs Shared



Basch: Clinical Trials, 2015

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Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

Developed under contracts to the NCI

(2008-11; 2011-2015; 2018-present)

http://appliedresearch.cancer.gov/pro-ctcae

PRO-CTCAE Symptom Library

78 adverse events (10% of CTCAE)

Generic item structures

Up to 3 domains per AE: frequency, severity, interference with daily activities

Patient-Centered Structure for Questions

CTCAE/MedDRA Term	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated

Two Items	Responses
What was the severity of your MOUTH OR THROAT SORES at their worst?	None Mild Moderate Severe Very Severe
How much did MOUTH OR THROAT SORES interfere with your usual activities?	Not at all A little bit Somewhat Quite a bit Very much

Qualitative Testing

Quality of Life Research
February 2014, Volume 23, Issue 1, pp 257–269

Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Hay/Basch: Qual Life Res. 2014 Feb;23(1):257-69

Quantitative Testing

Validity, reliability, responsiveness (n=940)

- Tested at individual item level

Dueck/Basch: JAMA Oncol. 2015 Nov;1(8):1051-9

Industry Trial Example

Cabozantinib vs. mitoxantrone
in metastatic prostate cancer

- 10 PRO-CTCAE AEs
  - Administered every 3 weeks from home between visits via automated telephone system
  - Human reminder call if no response after 72 hours
- Average **96% compliance** at each time point

Basch: Eur Urol 2018

Between-Arm Comparison: CTCAE

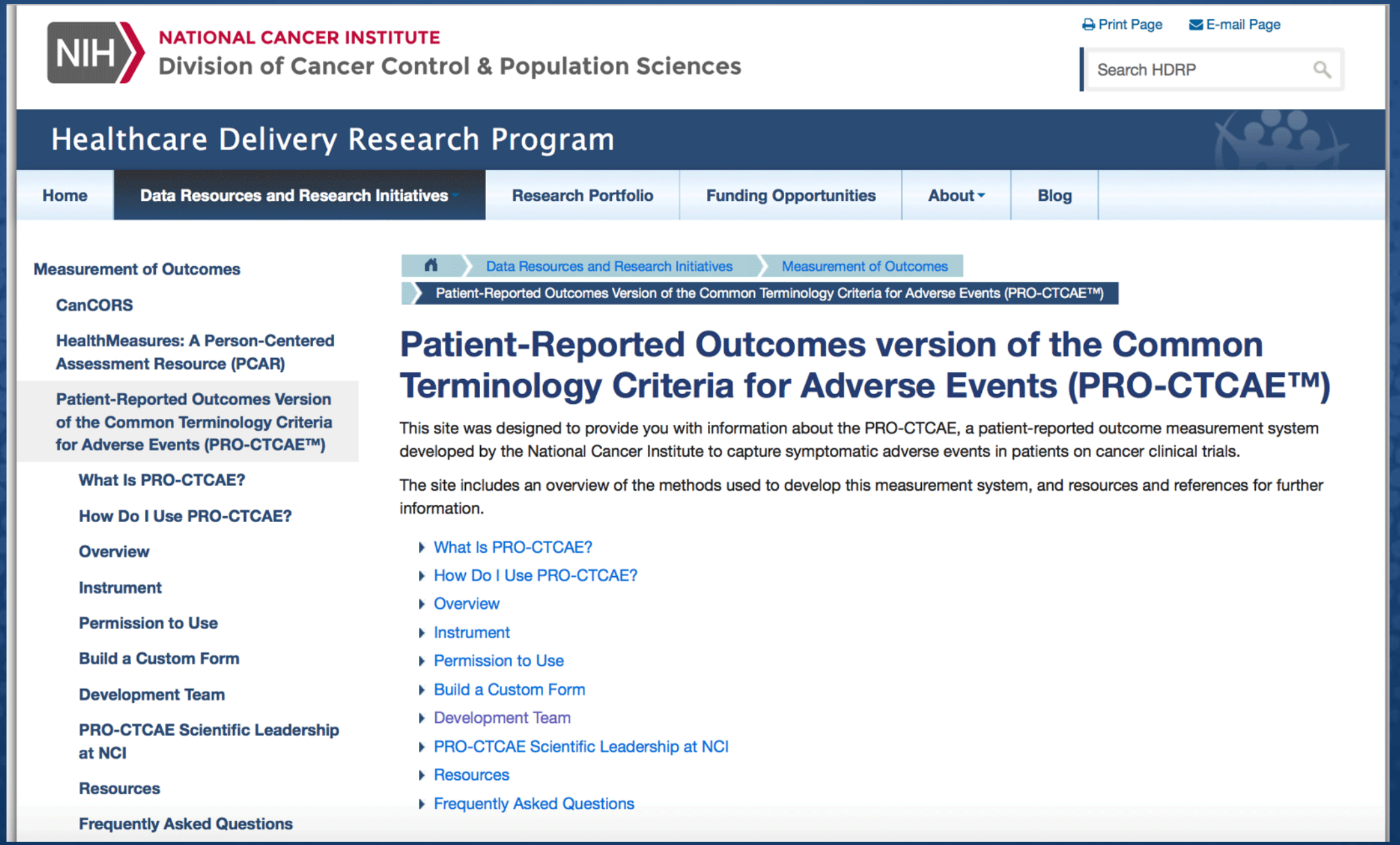
SYMPTOM	INVESTIGATOR-REPORTED *CTCAE Max Grade 3+*		
	Cabo	**Mito**	***P***
Constipation	3.3%	1.8%	1.00
Decrease appetite	1.7%	5.3%	0.36
Diarrhea	8.3%	1.8%	0.21
Fatigue	18.0%	8.8%	0.18
Nausea			
Short of breath	--	5.3%	0.11
Vomiting	1.7%	7.0%	0.20

Basch: Eur Urol 2018

Between-Arm Comparison: CTCAE *and PRO-CTCAE*

SYMPTOM	INVESTIGATOR-REPORTED *CTCAE Max Grade 3+*			PATIENT-REPORTED *PRO-CTCAE Max 3+*		
	Cabo	**Mito**	***P***	**Cabo**	**Mito**	***P***
Constipation	3.3%	1.8%	1.00	26%	13%	0.09
Decrease appetite	1.7%	5.3%	0.36	38%	15%	0.008
Diarrhea	8.3%	1.8%	0.21	44%	11%	<0.001
Fatigue	18.0%	8.8%	0.18	36%	26%	0.30
Nausea				38%	15%	0.008
Short of breath	--	5.3%	0.11	14%	13%	1.00
Vomiting	1.7%	7.0%	0.20	12%	7%	0.52

Basch: Eur Urol 2018



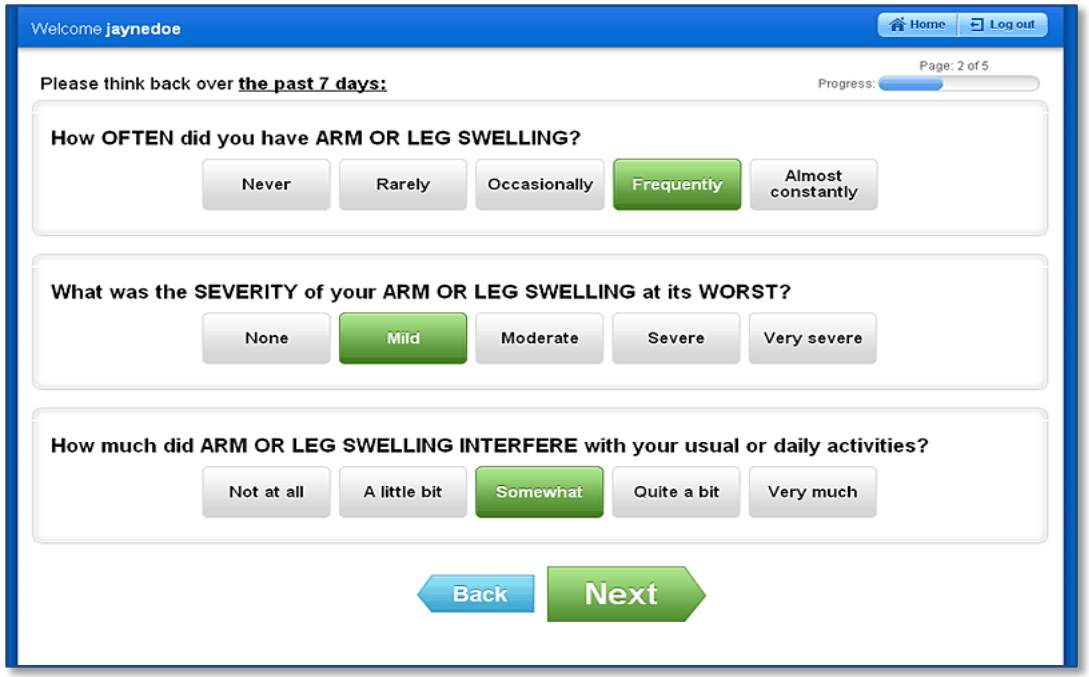
http://healthcaredelivery.cancer.gov/pro-ctcae/

What about Routine Care Patient Monitoring?

Toxicities/Symptoms of disease are common in oncology

Prior research shows PRO monitoring can improve communication, symptom management, QOL

Snyder: Qual Life Res 2012:1305; Kotronoulas: JCO 2014;32:1480; Detmar: JAMA 2002;288;3027; Velikova: JCO 2004;22:714



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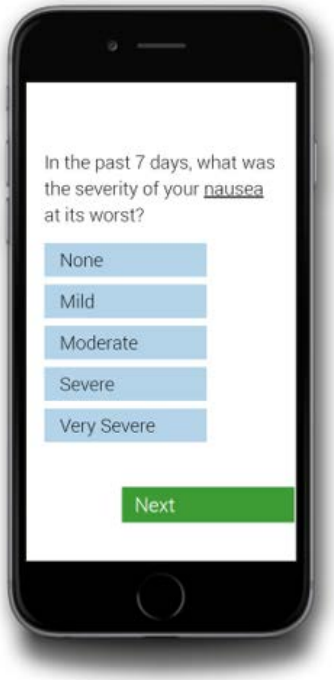
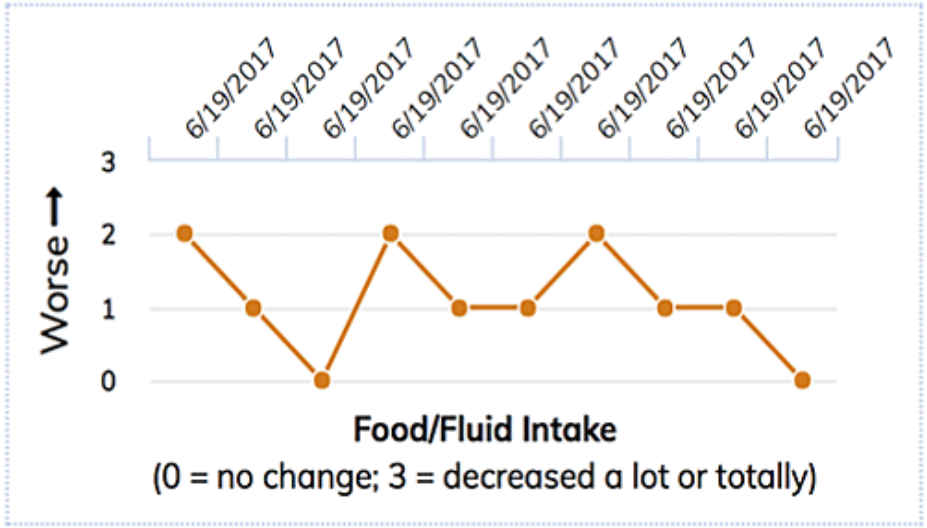


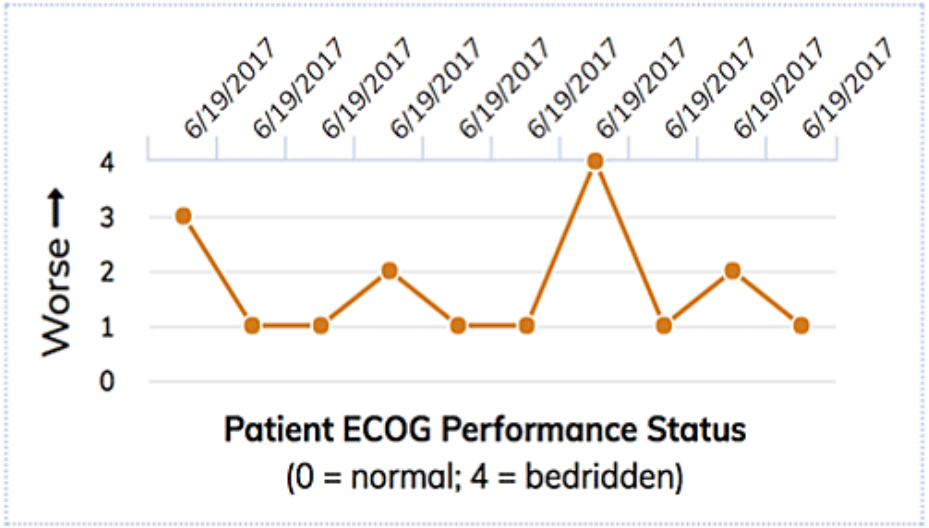
Mobile

Automated Telephone Systems

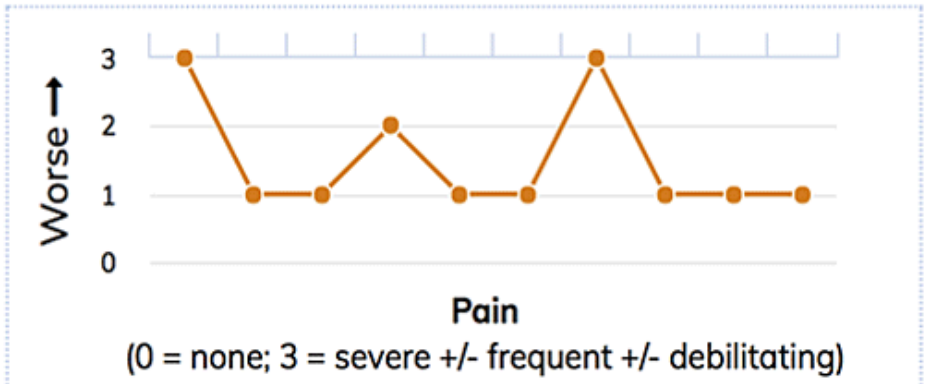
- **Severe symptoms on 6/19/2017:** Activity Level, Appetite, Nausea, Vomiting, Dyspnea, Diarrhea, Constipation, Pain, Insomnia, Depression.
- **Worsened symptoms between 6/12/2017 and 6/19/2017:** Activity Level, Appetite, Nausea, Vomiting, Dyspnea, Diarrhea, Constipation, Pain, Insomnia, Depression.
- **Falls:** 6/12/2017
- **Improved symptoms between 6/12/2017 and 6/19/2017:** Activity Level, Appetite, Nausea, Vomiting, Dyspnea, Diarrhea, Constipation, Pain, Insomnia, Depression.



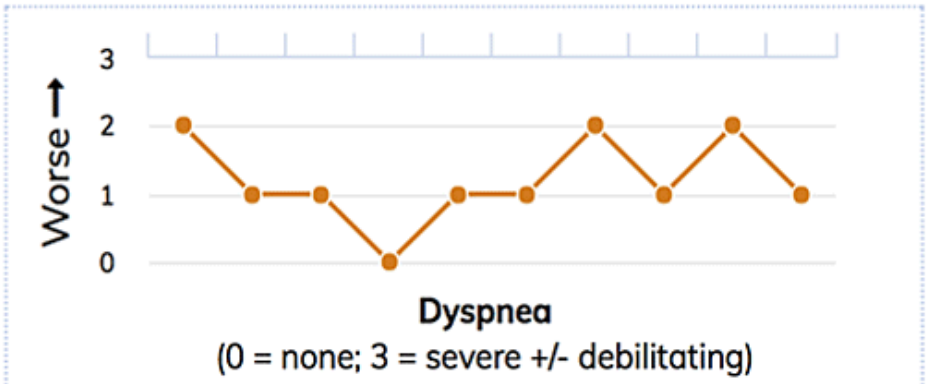
Food/Fluid Intake
(0 = no change; 3 = decreased a lot or totally)



Patient ECOG Performance Status
(0 = normal; 4 = bedridden)



Pain
(0 = none; 3 = severe +/- frequent +/- debilitating)



Dyspnea
(0 = none; 3 = severe +/- debilitating)

Alerts to Clinical Team *(Usually to a Nurse)*

From: Patient Symptom Tracking <webmaster@mskcc.org>
Date: Wednesday, June 14, 2010 at 2:16 PM
To: Microsoft Office User < [redacted]@mskcc.org>
Subject: Patient Symptom Alert

SYMPTOM REPORTED FROM HOME

Patient Medical Record Number: [redacted]
Date/Time Reported: 07/14/2010 at 2:15 PM

Symptom: DYSPNEA **Grade:** 3

Symptoms that have worsened since 07/07/2010:
Symptom: DYSPNEA from **Grade:** 1 to 3

Link to FULL REPORT

What can I do to manage my **sleep problems**?

Tips to help you sleep:

- **Tell your cancer care team about problems that are getting in the way of your sleep.** Getting treatment to lower side effects such as pain or bladder or bowel problems may help you sleep better.
- **Set good bedtime habits.**
  - Go to bed only when sleepy, in a quiet and dark room, and in a comfortable bed.
  - Go to bed and wake up at the same time.
  - Avoid napping if possible.
  - Make sure your bedroom is not overly hot or cold.
  - Stop watching television or using devices with screens a couple of hours before going to bed.
    - Devices like: iPads, laptops, and smart phones.
  - Don't drink or eat a lot starting about 2-3 hours before bedtime.
  - Exercising too close to bedtime may make sleep more difficult.
    - Exercise before 2:00pm promotes sleep.
  - Don't watch the clock at night.
  - Keep out pets who wake you up.

- **Don't stay awake in bed** for more than 5-10 minutes. If you do not fall asleep, get out of bed, sit in a chair in the dark until you are sleepy. It's okay if this happens several times a night.
- **Avoid caffeine after midday.** Also cigarettes, alcohol and some 'over-the-counter' medications may interfere with sleep.
- **Sleep medicine may be prescribed** by your cancer care team for a short period if other strategies don't work.
- **Cognitive behavioral therapy (CBT) and/or relaxation therapy may help.** For example, a CBT therapist can help you learn to change negative thoughts and beliefs about sleep into positive ones.
  - Muscle relaxation, guided imagery, and self-hypnosis may help.

PAIN

Pain is common in patients with cancer and impacts patients' functional status and quality of life.

- Cancer patients often have multiple sites of pain.
- Cancer pain is associated with increased emotional distress and risk of developing depression.

Sources of pain in cancer patients include:

- Direct effects of cancer (bone pain, pressure on internal organs, ascites).
- Surgery pain.
- Radiation therapy (mucositis, dermatologic changes, brachytherapy pain, mucosal inflammation).
- Chemotherapy or targeted therapy (arthralgia, myalgia, neuropathy, bowel function changes, mucositis, rash).
- Diagnostic procedures.
- Other health conditions (arthritis, osteoporosis)

Assessment

- Assess pain medication history.
  - What is prescribed, what is the patient actually taking, how it is working?
  - Is the patient taking opioids, and are they long acting, short acting, or both?
  - How long has the patient been on their pain regimen?
- Conduct comprehensive pain assessment:
  - Location of pain (Where does pain originate? Does it radiate to another area of the body?).
  - Intensity of pain (use pain scale of 0-10 with 10 being the worst pain imaginable).
  - Quality of pain (sharp, stabbing, burning, aching).
  - Using scale of 1-10 with 10 being the worst pain imaginable: What is your pain at its best? What is it at its peak? What is your pain after taking your pain medications?
  - Assess for breakthrough pain (Does the pain return or increase in intensity before the next dose?).
  - Onset, duration and aggravating/alleviating factors (When does it start? What makes it worse/better? How often does it occur? How long does it last?)
- Assess for changes in activity level, sleep, general activities of daily living, depression.
- If taking opioids, assess for constipation.

Severity

Grade 1 *Mild*	Grade 2 *Moderate*	Grade 3 *Severe*	Grade 4 *Life Threatening*
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care, ADL	

Interventions Based on Severity

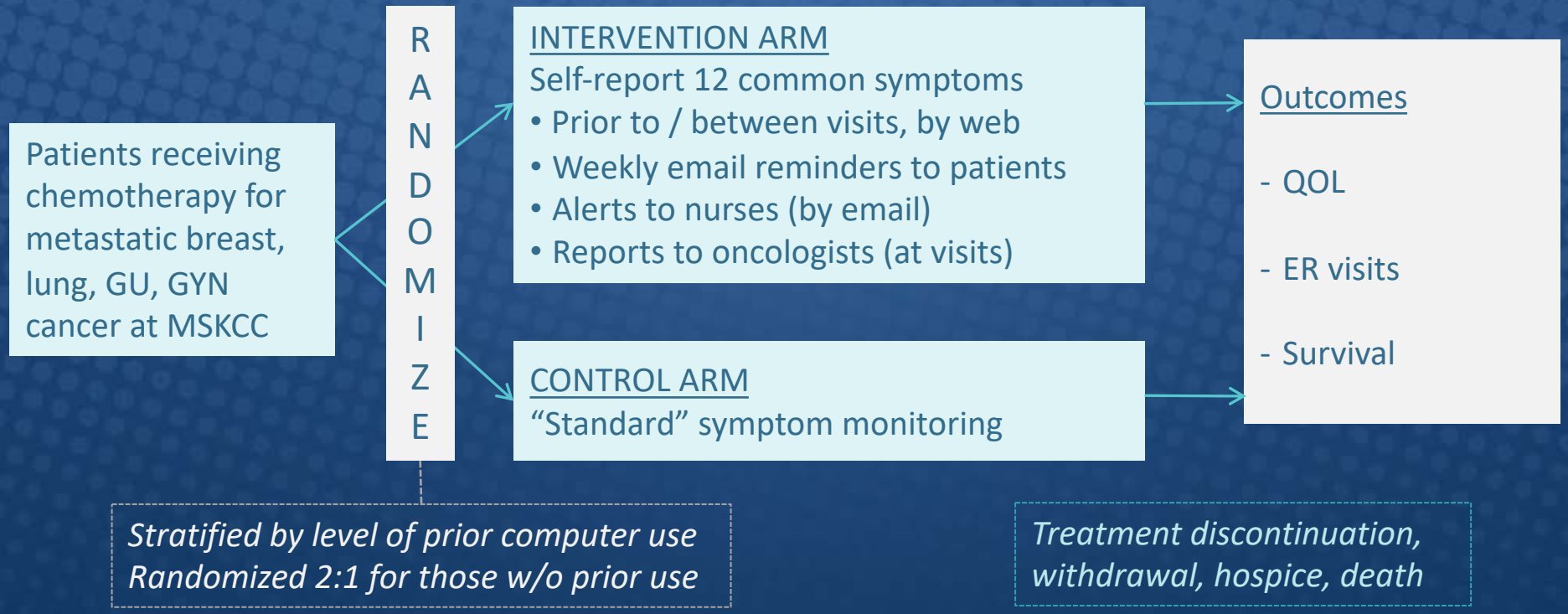
Management of Pain:

1. Non-opioids (acetaminophen, COX-2 inhibitor, NSAID). Note that COX-2 inhibitor (celecoxib, meloxicam) does not inhibit platelet aggregation; NSAID toxic effects can include acute renal failure, gastrointestinal toxicity, cardiovascular toxicity, and CNS toxicity such as memory loss and confusion. NSAIDs should be avoided or used with caution if patient has: stomach or intestinal ulcers; cardiovascular disease and/or hypertension; kidney disease; bleeding disorders; pregnancy; taking other prescription anti-coagulants such as warfarin (Coumadin) or heparin, phenytoin (Dilantin), and/or cyclosporine; use of acetaminophen may cause hepatic injury; use caution with liver disease.
2. Opioids such as morphine when pain persists or increases and cannot be controlled by non-opioids.
3. Non-medication treatments should be offered for all patients with pain. These include emotional support, distraction (music, social engagement), appropriate physical activity (positioning, cushioning, supportive devices, exercise. Physical therapy), and topical application of heat or cold.

Considerations:

- Pain medication scheduled "around the clock" when pain is constant. Consider long-acting agent.
- Use the simplest route of administration possible.
- Consider additional supportive drugs to address anxiety, depression, or neuropathic pain symptoms.
- Provide patient/family/caregiver education about treatment approaches and safe medication use.
- Consider suggesting a pain diary to monitor characteristics of pain, medication regimen, and response to medication.
- No driving when using opioids.

MSKCC "STAR" Study: Impact on Clinical Outcomes



Basch: JAMA, 2017; JCO 2016; ASCO 2017

MSKCC “STAR” Study: Impact on Clinical Outcomes

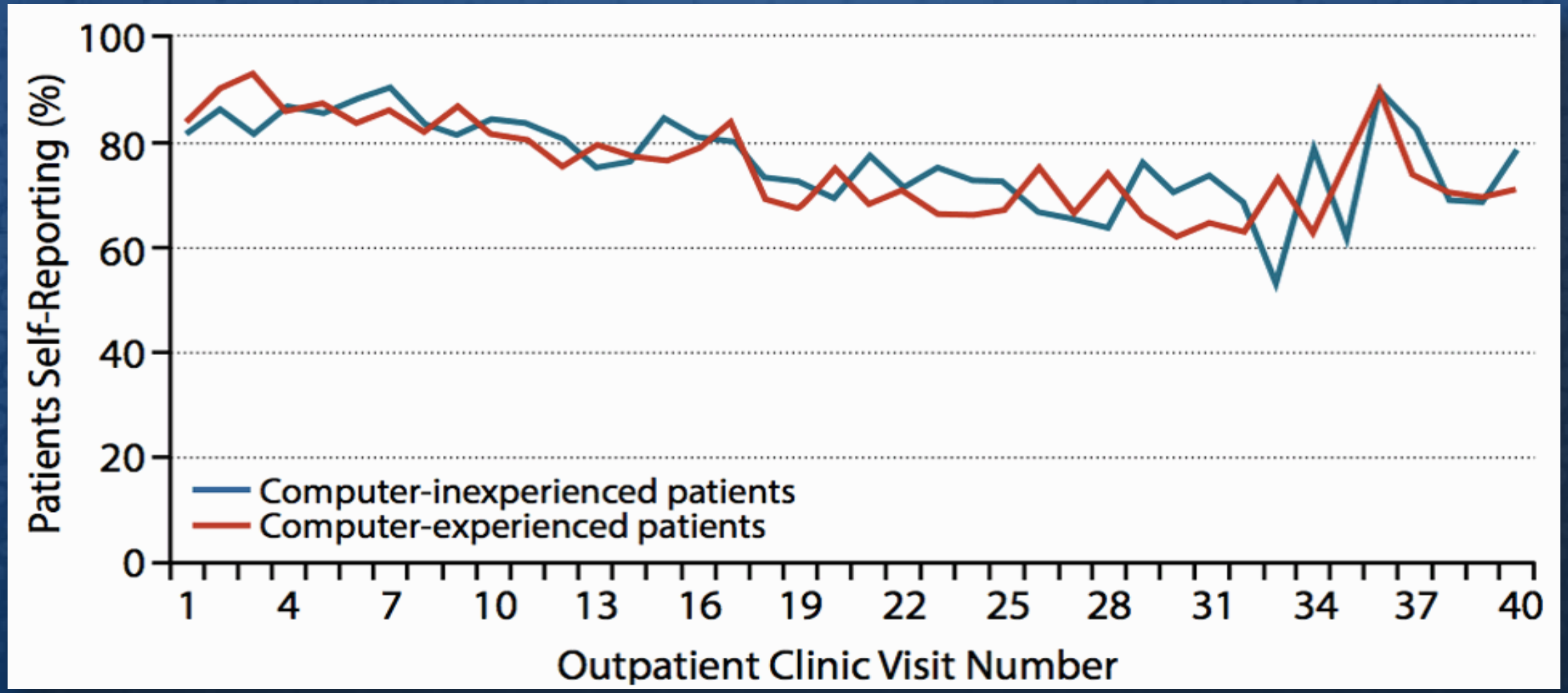
766 patients enrolled between June 2007 and January 2011

Followed to analysis in June 2016

- Median follow-up 7 years
- 517/766 (67%) participants had died

Basch: JAMA, 2017; JCO 2016; ASCO 2017

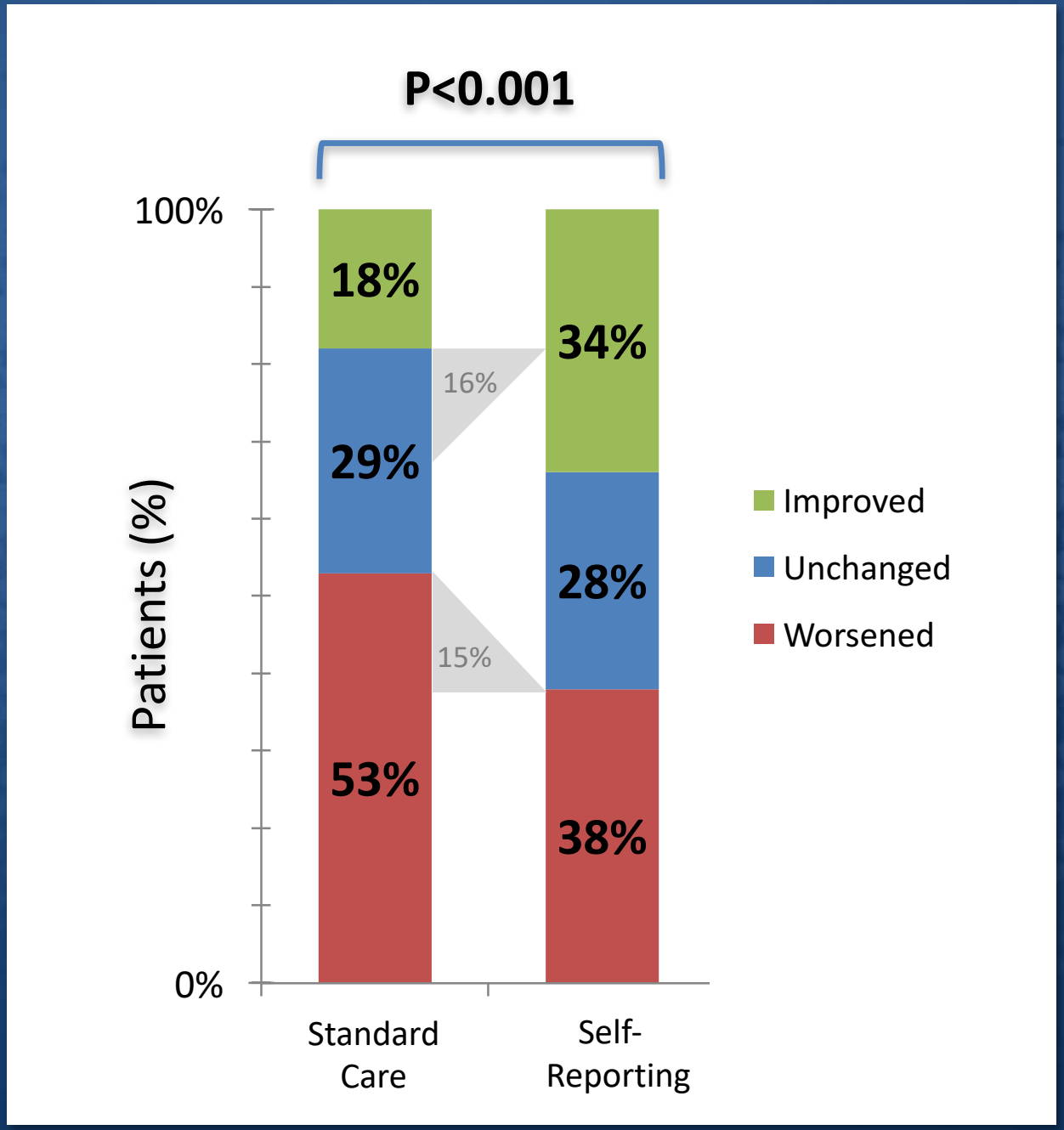
Feasibility



Basch: JAMA, 2017; JCO 2016; ASCO 2017

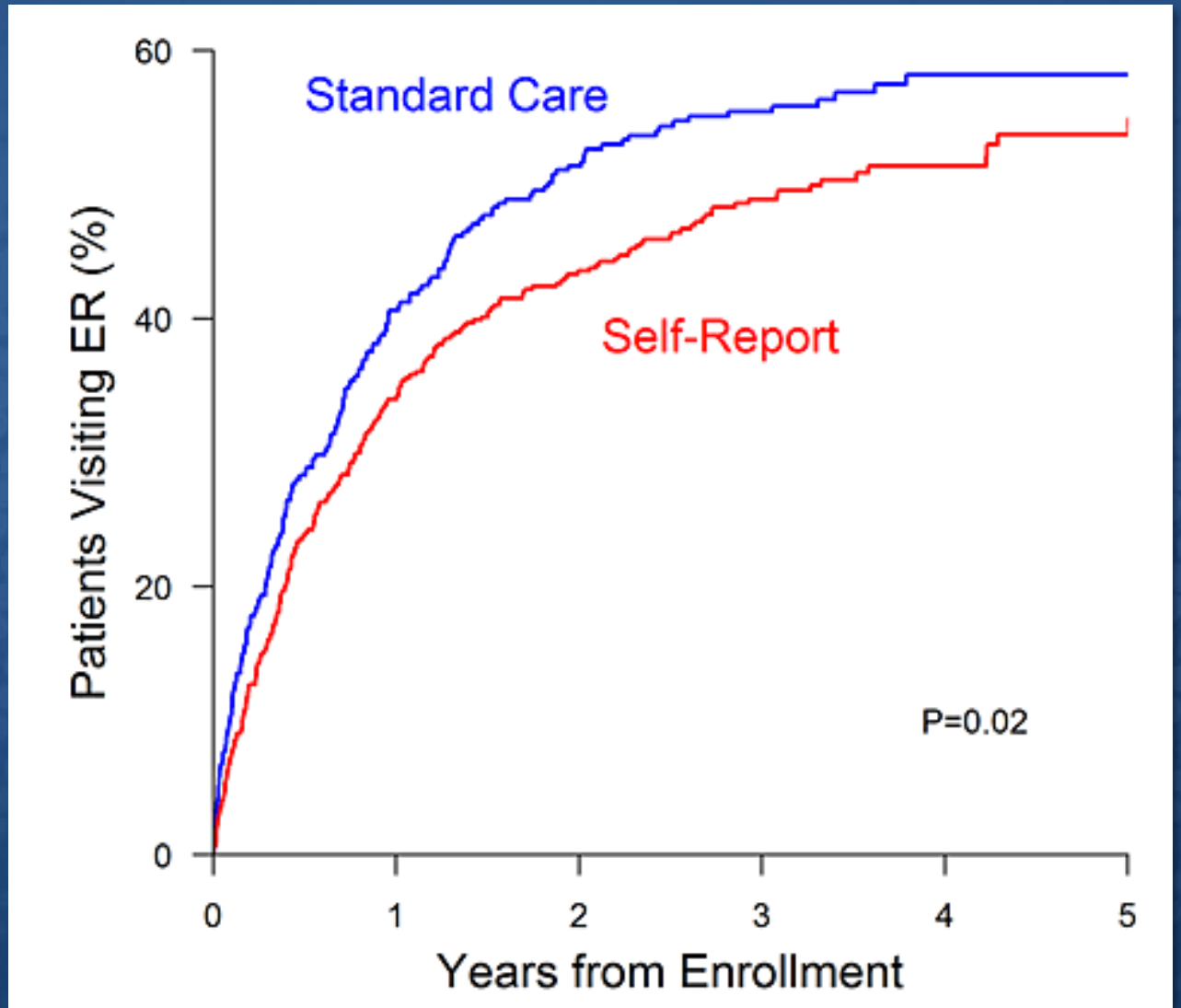
Quality of Life

- Assessed at 6 months, compared to baseline
- Compared to standard care, 31% more patients in the self-reporting arm experienced QOL benefits (*P<0.001*)



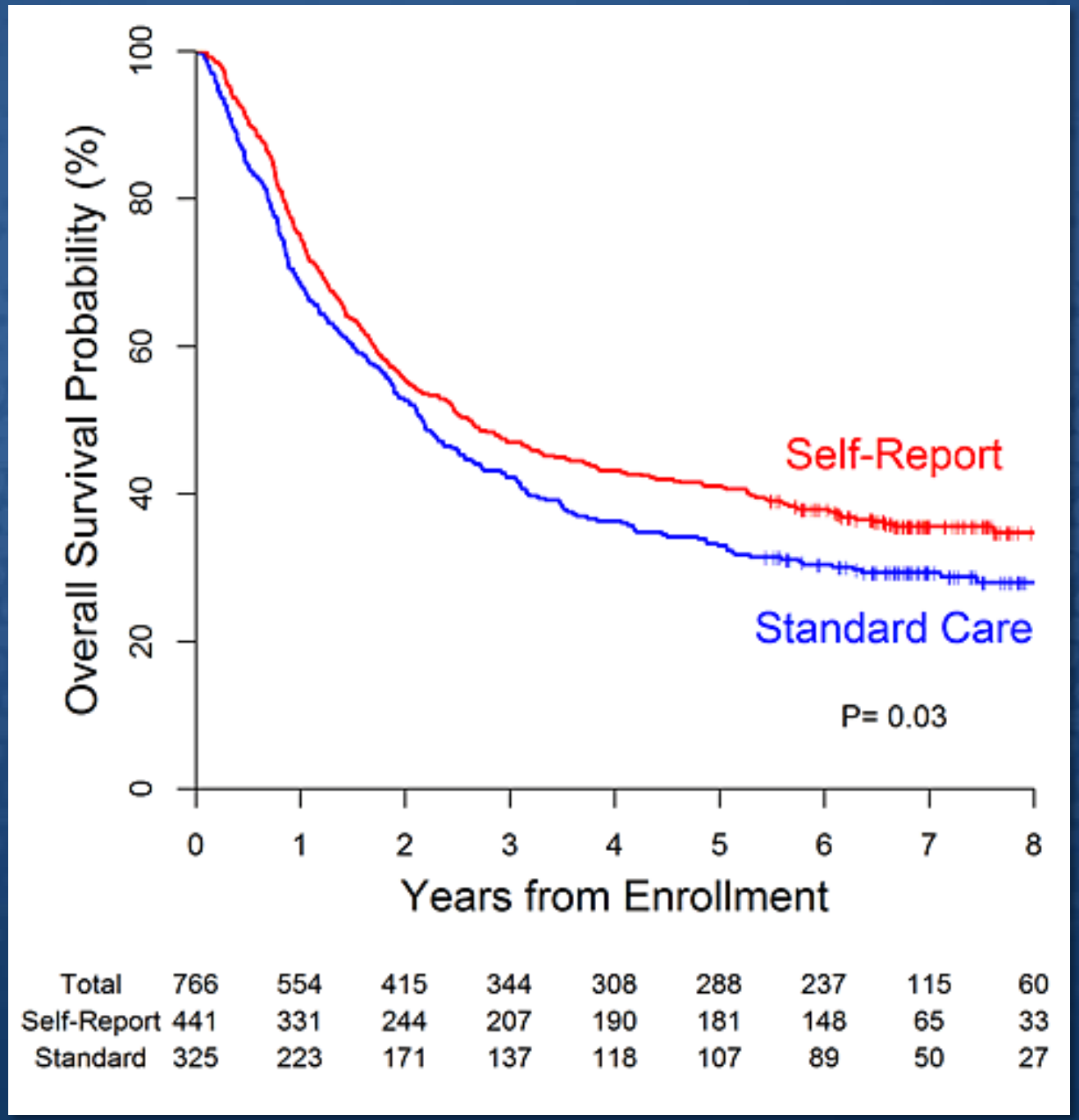
Emergency Room Visits

- Compared to standard care, 7% fewer patients in the self-reporting arm visited the Emergency Room, with durable effects throughout the study (*P=0.02*)



Overall Survival

- Compared to standard care, median survival was 5 months longer among patients in the self-reporting arm (31.2 vs. 26.0 months) (*P=0.03*)
- Remained significant in multivariable analysis:
  Adjusted hazard ratio 0.832
  (*95% CI; 0.696, 0.995*)
- 5-year absolute survival benefit of 8%



Mechanisms of Action

1. Proactive monitoring prompts clinicians to intervene early, before symptoms worsen and cause serious downstream complications
   - *Nurses acted on >75% of PRO alerts*
2. Symptom control enables patients to stay more functional, which is known to be associated with better survival
   - *Better physical functioning in PRO arm (P=.01)*
3. Symptom monitoring enables control of chemotherapy side effects, enabling more intensive and longer duration of cancer treatment
   - *Longer time on chemotherapy in PRO arm (8 months vs. 6 months)*

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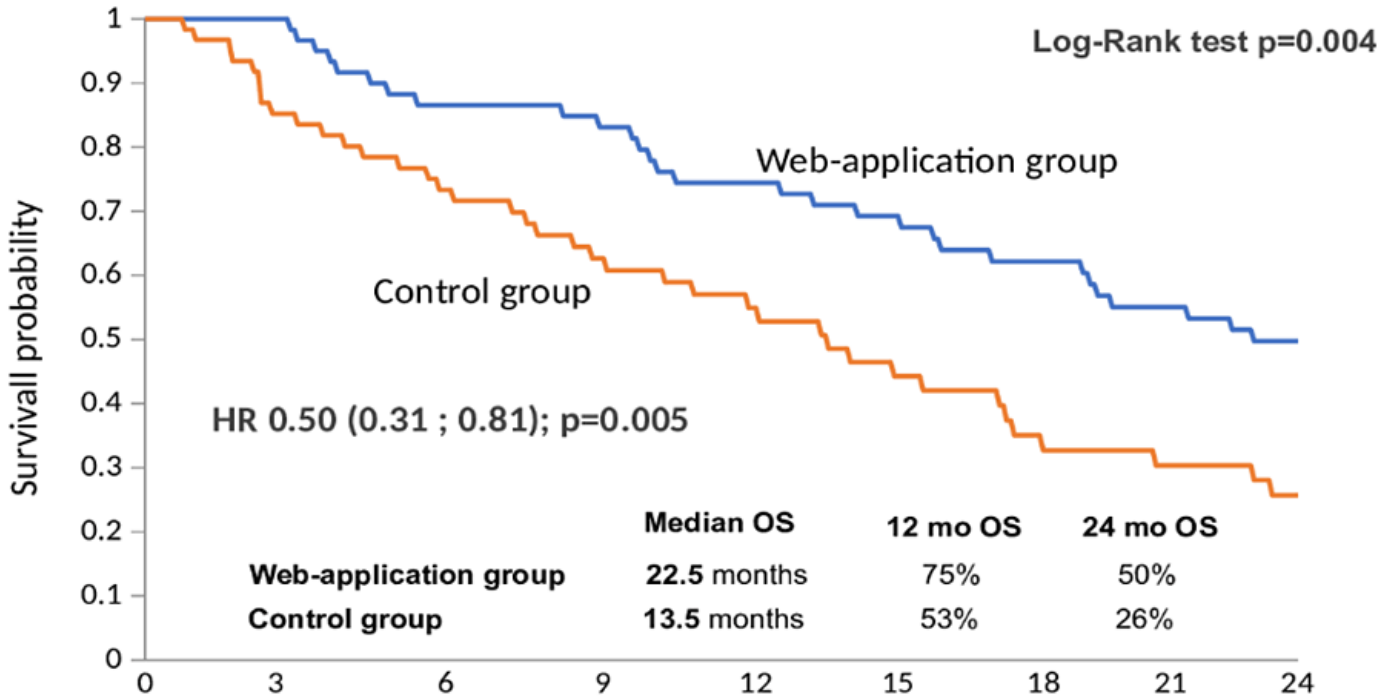
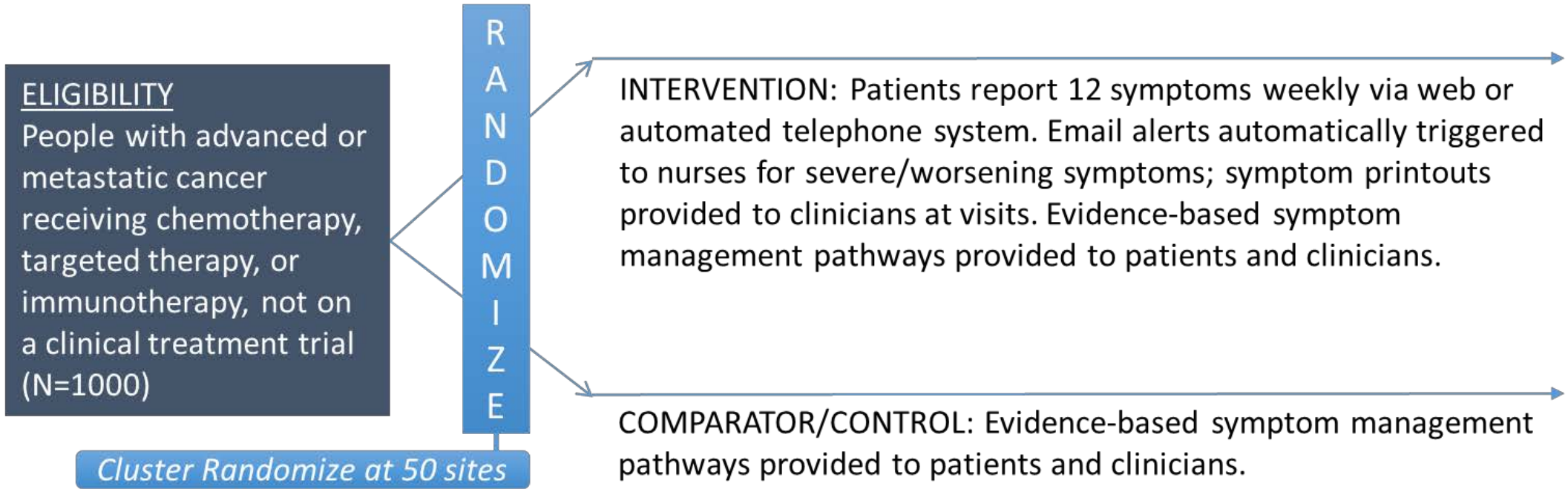
Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer

Fabrice Denis, MD, PhD[1]; Ethan Basch, MD[2]; Anne-Lise Septans, PhD[3]; et al



PRO-TECT
Cancer Symptom Study



Open at 52 US sites, ~ 1000 patients enrolled to date

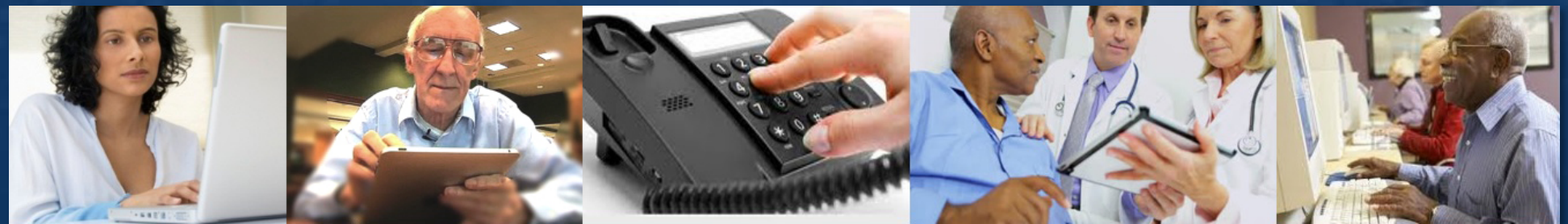
Conclusions

Patient self-reporting improves monitoring of toxicities/symptoms and outcomes in trials and routine care

- Expands our understanding of patient experience
- Engages patients in research and care

Work ahead is in implementation

- Integration with EHR systems and clinical pathways
- Coordination with palliative care and navigation programs



With Gratitude

UNC LINEBERGER

The patients and families participating in this research

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Patient representatives: Diane Paul, Cindy Geoghegan, Patty Spears, Mary Lou Smith, Patrick Gavin, Jane Perlmutter, Alliance Patient Representative Committee

MSK: Lauren Rogak, Alexia Iasonos, Mark Kris, Howard Scher, Paul Sabbatini, Tom Atkinson, Narre Heon, Marwan Shouery, Kevin Shannon, Kai Lin, Charmaine Pun, Roxana Damian, Sharon Bayuga, Jennifer Hay, Glenn Heller, Natalie Barragan (Prior: Cliff Hudis, Mary Shaw, Laura Sit, Allison Barz, Mike Fruscione, Sean Ryan, Dawn Lavene, Liora Stark, Mark Appawu, Lisa Cianci)

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Research networks: Alliance/CALGB; RTOG/NRG; NCCCP (now NCORP)

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