

Analysis of a Multisite Randomized Clinical Trial of Massage Therapy

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M & A Seminar

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Outline

- **REST study description**
- **Unique Components of Trial**
 - **Active Control Group**
 - Selection
 - Implications for study implementation and analysis
 - **Measurement of immediate and sustained effects**
 - **Intention to treat – design and analysis**
 - **Qualitative study**
 - **Secondary analyses**

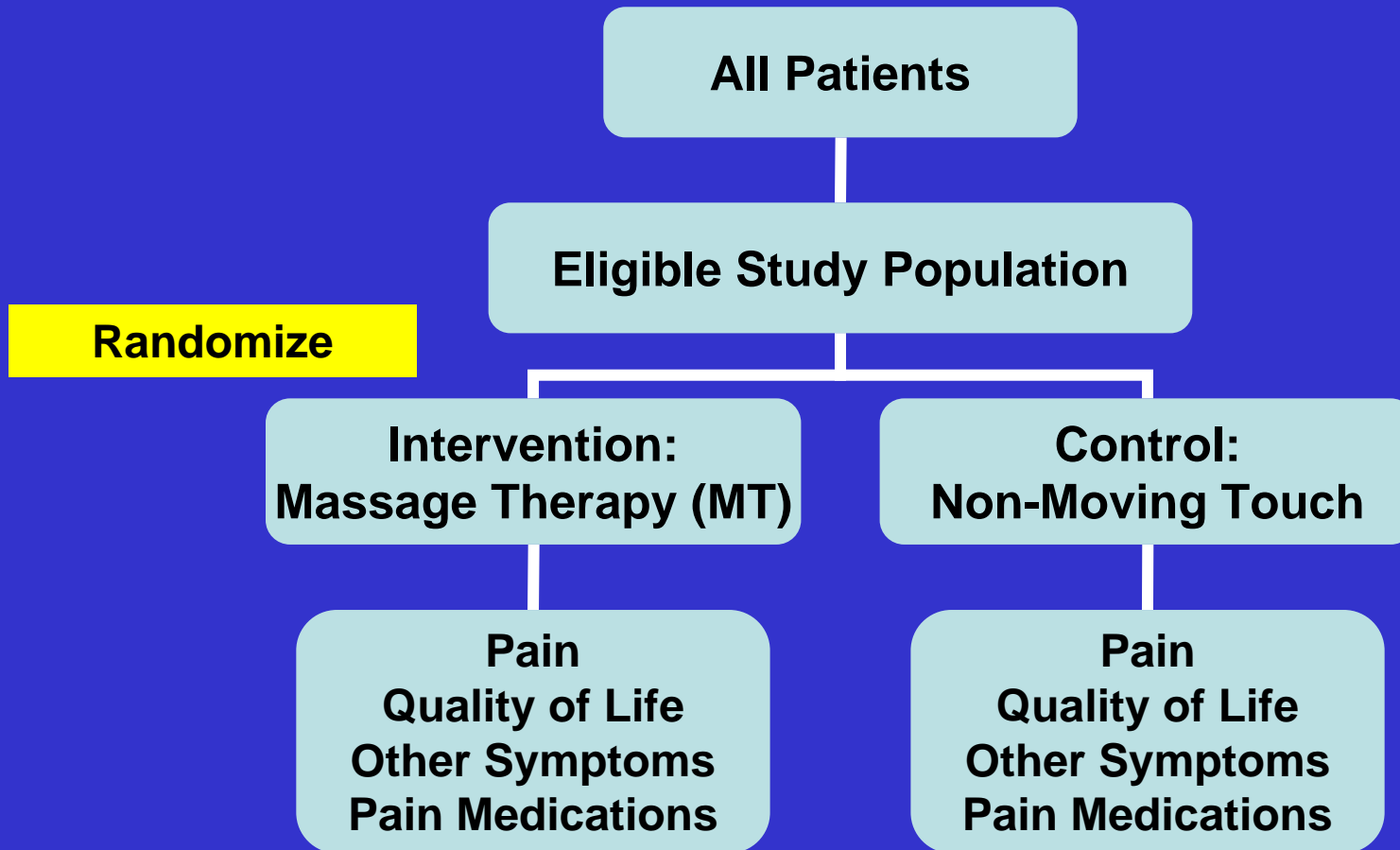
“REST” Study

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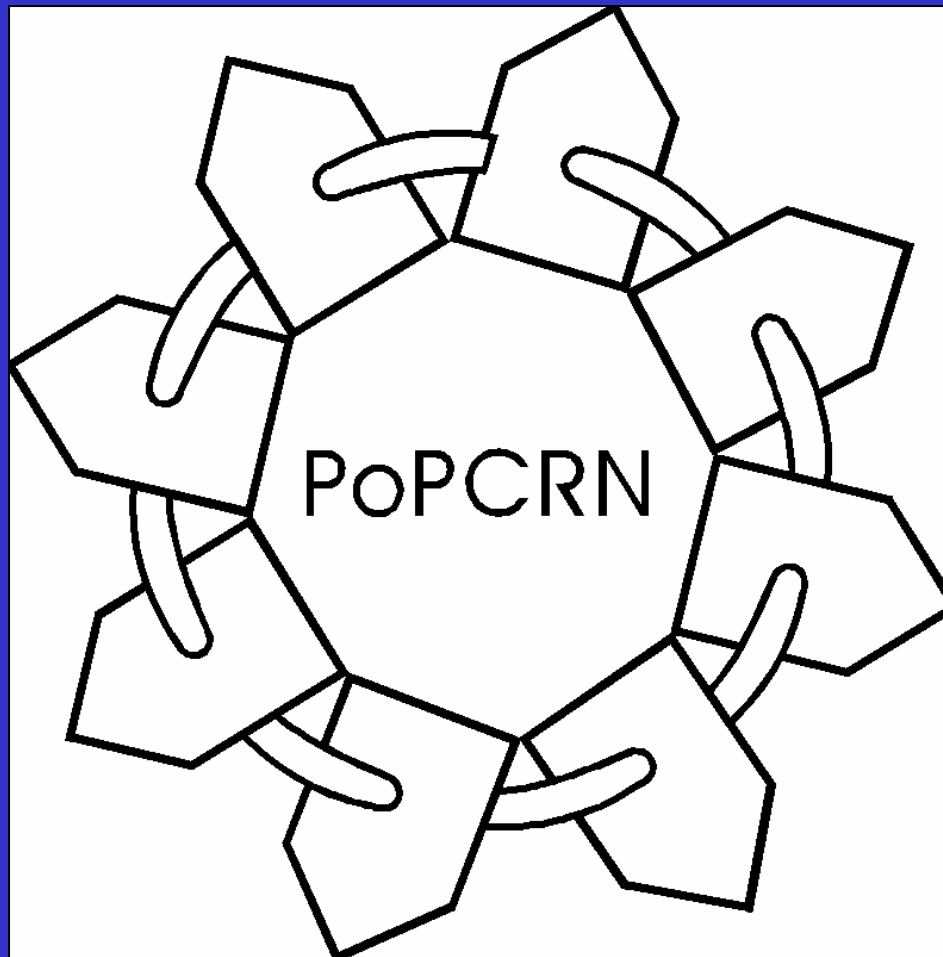
“Reducing End-of-life Symptoms with Touch”



Study Design: Multi-site RCT

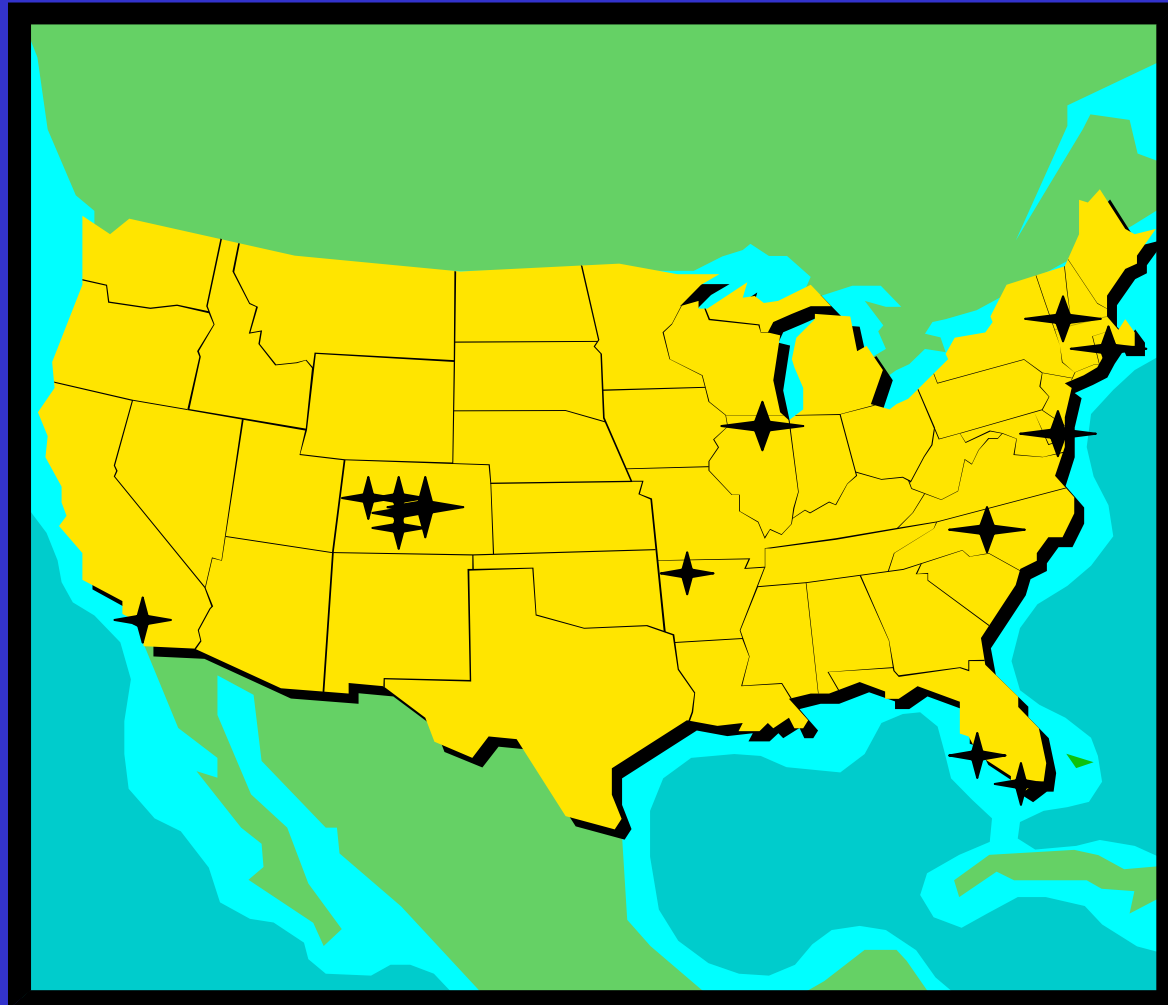


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15 Study Sites: Members of PoPCRN Network





Eligibility Criteria

- **Inclusion**
 - English-speaking
 - Age \geq 18 years
 - Diagnosis of advanced cancer
 - At least moderate pain (score \geq 4) in the prior week
 - Anticipated life expectancy \geq 3 weeks
 - Consent and are able to participate in study
- **Exclusion**
 - Professional massage in prior 4 weeks
 - Anticoagulants
 - Platelet count $<$ 10,000
 - Unstable spine



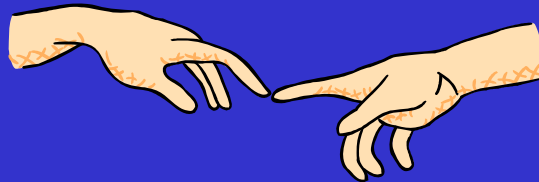
Active Control

The Control Condition

- All factors except the active ingredient of the treatment being tested are held constant
- The control condition should be as structurally indistinguishable from the treatment condition as possible

Selecting the Control Condition

- Isolate therapeutic effects of massage from non-specific therapeutic effects of attention and touch
- Isolate massage from usual combination with other therapies (music, heat, essential oils)
 - Studies that do not address treatment specificity through creating a structurally equivalent group show larger between group differences.



Massage Therapy Trials: A Variety of Control Conditions

- Relaxation techniques
- Electrical stimulation
- Psycho-educational group or therapeutic interaction with a care provider
 - controls for natural history, placebo and attention/ time
- Other therapies (chiropractic or acupuncture)
- Sham laser
 - controls for the placebo effect
- Usual care/standard treatment
 - controls for the natural history of disease

Touch, in itself, can produce a non-specific effect - to control for this effect and natural history, placebo and attention, a form of touch other than massage needs to be employed for control group.

Criteria for Structuring Control Conditions

- 1) Equivalent contact
- 2) Similarity of form
- 3) Minimize adverse/negative effects
- 4) Minimize therapeutic benefit
- 5) Equivalent expectation of therapeutic benefit

Comparison of Control Conditions

Control Condition	Contact	Form	Minimum Negative Effects	Minimum Benefit	Expectations
Relaxation	-	-	+	-	+
Other mind-body	-	-	+	-	+
Electrical stimulation	-	+	+	-	+
Chiropractic, manipulation, acupuncture	+	+	+	-	+
Therapeutic interaction	+	-	+/-	+/-	+/-
Friendly visit	+	-	-	+	-

Control Condition	Contact	Form	Minimum Negative Effects	Minimum Benefit	Expectations
Usual care	-	-	+	+	-
Comfort touch	+	+	+	-	+
Therapeutic touch	+	+	+/-	-	+/-
Psycho-educational group	-	-	+	-	+
Sham laser	-	-	+	+	+
Non-moving touch	+	+	+	+/-	+/-

“Non-Moving Touch”



- Parallels massage condition in length of encounter (30 minutes of hands-on time) and number of treatments (6 treatments over a 2 week period)
- Similar in form to massage therapy - involves physical contact with the body

“Non-Moving Touch”

- Laying the hands on 10 different body locations
 - Base of the neck, shoulder blades, lower back, calves, heels, then clavicles, forearms, hands, knees and feet
- 3 minutes at each location
 - Sequencing of the locations mimicked typical structure for massage therapy: from supine position head to toe to the prone position from head to toe.
- Provided by individuals with no body or energy-work training.



Intervention and Control Exposures

Intervention: Massage Therapy (MT)

- Gentle effleurage, petrissage and myofascial trigger point release
- Six 30 minute sessions, at least 24 hours apart, over 2 week period
- Biotone massage crème
- No music, talk or aromatherapy

Control

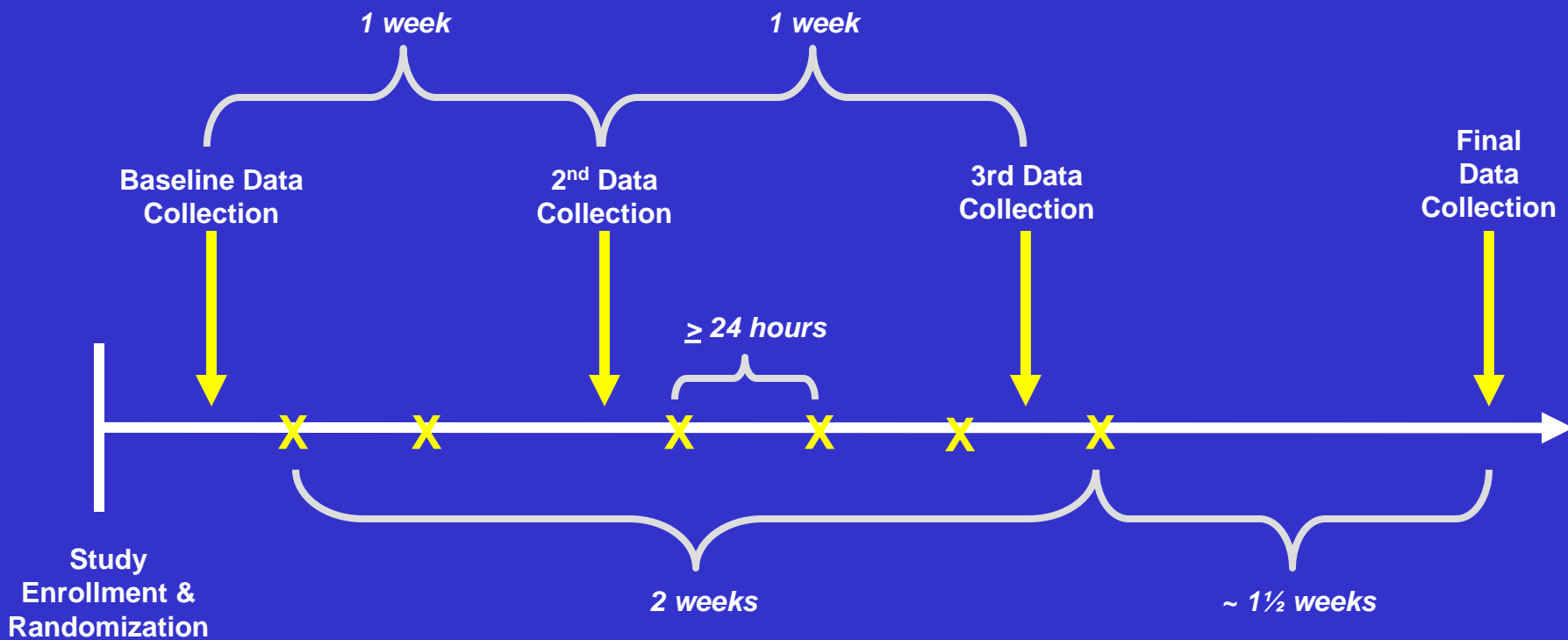
- Same timing and conditions as MT
- 3 minutes of non-moving touch at 10 defined body locations
- Disruption of “healing intent”
- Control for time, attention and touch

Active Control - Implications for implementation and design

- Implementation
 - On site staff recruitment and training
 - Recruitment
 - Blinding
- Sample size
 - Active control will produce some change, thus smaller difference between the groups
 - Prohibited a 3-arm study

Immediate and Sustained Effects

Sample Participant Timeline



Data Collection

FREQUENCY	INFORMATION COLLECTED
Baseline	Demographics Expectation of benefit Neuropathy Pain Scale (NPS) Brief Pain Inventory (BPI) Memorial Symptom Assessment Scale (MSAS) McGill Quality of Life (MQOL) Karnofsky Performance Scale (KPS) Medications for symptoms relief “Usual care”
“Immediate Effect” (Prior to & following each treatment session)	Heart rate, Respiratory rate, Memorial Pain Assessment Card (MPAC – pain and mood)
“Sustained Effect” (Weekly x 3)	BPI, MSAS, MQOL, KPS, Medications, “Usual care”

Analytic Issues

- Immediate and Sustained Effects
 - Repeated correlated outcomes => Repeated measures model
 - 12 (2*6) potential immediate measures, reduced to 6 pre-to-post changes
 - Tested for time-trends within post-baseline assessments; negative results allow us to use simple summary measures
 - Immediate: Average pre-post differences
 - Sustained: Average post score- baseline

Other Analytic Issues

509 Assessed For Eligibility

129 Excluded
71 did not meet inclusion criteria
53 refused to participate
5 enrolled and consented, not randomized

380 Randomized
and included

**188 ASSIGNED TO MASSAGE
THERAPY (MT)**

**16 DISENROLLED PRIOR TO ANY
TREATMENT OR ASSESSMENT**

Death: 2
Premature, alive: 11
Other/scheduling: 3

Assessments

108 received all 4 assessments
63 received 1 – 3 assessments
1 data collection packet lost, no data

MT Treatments

113 received all 6 MT treatments
28 received 1 – 5 MT treatments

192 ASSIGNED TO CONTROL

**15 DISENROLLED PRIOR TO ANY
TREATMENT OR ASSESSMENT**

Death: 4
premature, alive: 7
other/scheduling: 4

Assessments

96 received all 4 assessments
81 received 1 – 3 assessments

Control Treatments

93 received all 6 Control treatments
54 received 1 – 5 Control treatments

Analytic issues

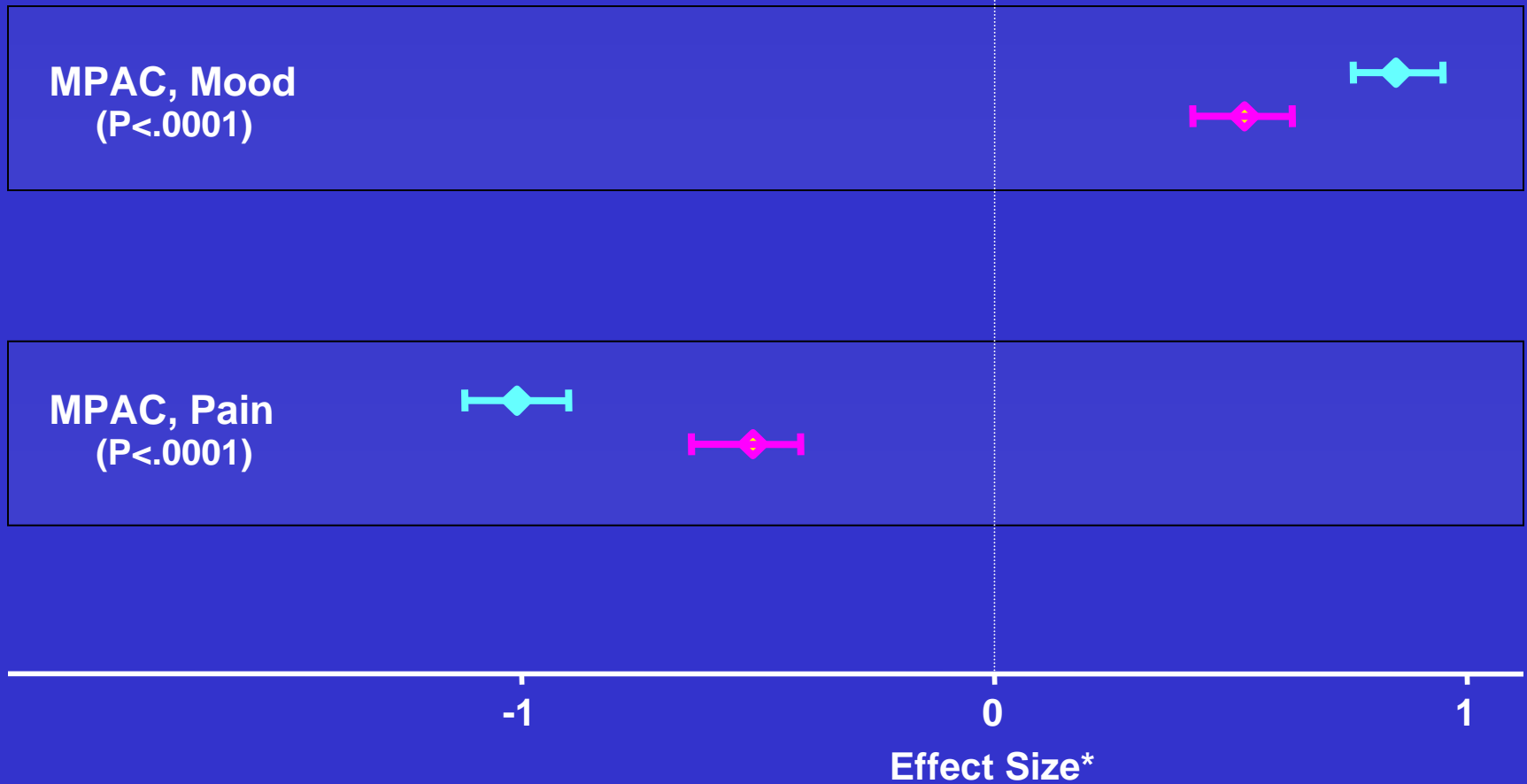
- Challenge of delivering all 6 ‘messages’
 - Intent-to-treat analysis (as randomized)
 - Follow-up continues if at all possible
 - Intermediate outcomes
- High likelihood of “dropout”
 - Analysis must accommodate missing data
 - Assumption of MAR = Given previous assessments and covariates, dropout is unrelated to outcome

Analysis Overview

- Repeated measures model that accommodates incomplete **correlated** data
- Intention to treat analyses
- Models adjusted for:
 - Age, comorbid conditions, gender, prior massage therapy, worst pain in prior week at study entry, Karnofsky Performance Status
- Evaluated potential moderators:
 - Perceived efficacy of massage therapy
 - Presence of neuropathic pain
 - Presence of bony metastases
- Multiple instruments/Simple reporting and interpretation
 - Reported results as effect size
 - Summary measures



Immediate Beneficial Effect MT (—) vs. Control (—)

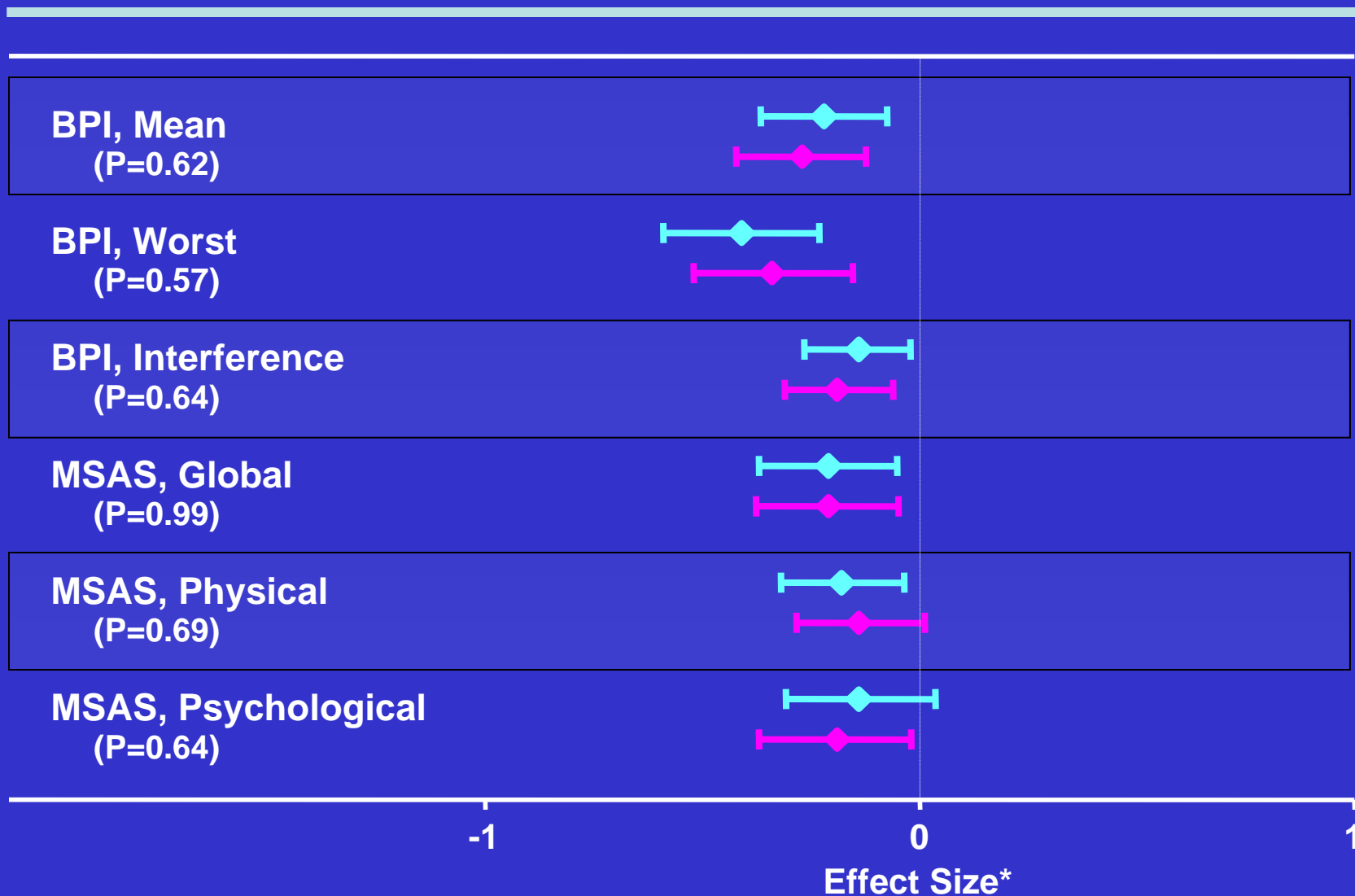


*Adjusted for age, comorbid conditions, gender, prior MT, worst pain in prior week, KPS



No Sustained Effect

MT (—) vs. Control (—)



*Adjusted for age, comorbid conditions, gender, prior MT, worst pain in prior week, KPS

Secondary Analyses

Secondary Analyses

- 6-10 secondary analyses planned
- Challenges (some of them ..)
 - Avoid 10 different subsets of the data
 - Consistency across variable definition
- Solutions
 - Centralized analysis plan
 - Team meetings
 - Obsessive/Compulsive data management (e.g. variables defined in analysis files used by all)
- Benefits
 - Made use of nearly all of the data
 - Gave each member of the study team an important role in drafting manuscripts

Qualitative analysis

REST Study Funding

- National Institutes of Health –National Center for Complementary and Alternative Medicine (1 R01 AT01006-01A2)
- Mendel/Asarch Lung Cancer Family Foundation Grants Program
- Paul Beeson Physician Faculty Scholars in Aging Research Award
- Robert Wood Johnson Generalist Physician Faculty Scholars Program



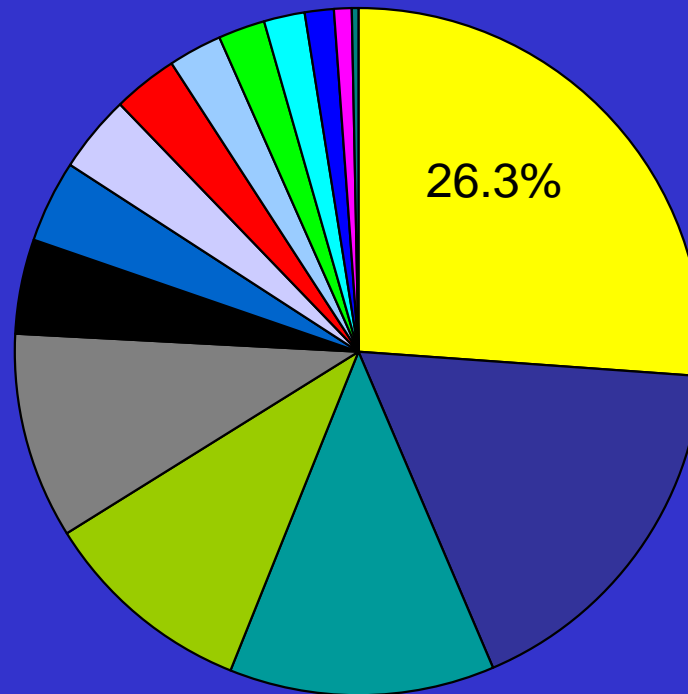
REST Study Team

- Marlaine Smith, RN, PhD (Co-investigator)
- Linnea Hemphill, RN (Co-investigator)
- Lisa Corbin, MD (Co-investigator)
- Karen Mellis, MS (Research Assistant)
- Sue Felton (Research Assistant)
- Traci Yamashita (Research Assistant)
- Brenda Beaty, MSPH (Data Analyst)
- Jeanette Ezzo, CMT, MPH, PhD (Consultant)
- Cindy Bryant, PhD (Consultant)
- William Henderson, PhD (Statistician)





Enrollment by Site



■ Pikes Peak

■ UCCC

■ Partners

■ Cape Cod

■ North Shore

■ Hope Hospice

■ San Diego Hospice

■ LifePath

■ Circle of Life

■ Community/DC

■ Hospice of St. John

■ Charlotte

■ Berkshires

■ Pathways

■ Catholic/Miami



Study Population Characteristics, N=380

CHARACTERISTIC	N (%)
Gender, Female	232 (61)
Race, White	348 (92)
Location	
Home	300 (79)
Hospice Facility	61 (16)
Nursing Home	14 (4)
Cancer Type	
Lung	95 (25)
Breast	64 (17)
Pancreas	35 (9)
Bone or Spine Metastases	102 (27)
Concomitant Medical Conditions	
Neurologic dx	30 (8)
Medical dx	167 (44)
Vascular dx	31 (8)
Neuropathic Pain Present	88 (26)

Study Population Characteristics, N=380

CHARACTERISTIC	Mean (SD)
Age, years	64.7 (14.4)
Years Post Cancer Diagnosis	2.7 (4.6)
Karnofsky Performance Scale	62 (15)
Current Pain Intensity	4.4 (1.7)
Worst Pain in Prior Week	7.8 (2.1)
Goal Pain Level	0.3 (0.8)
No. Body Areas with Pain	7.1 (6.5)

Baseline Brief Pain Inventory Scores (0 – 10, 10=worst pain)

	MT mean (SD)	Control mean (SD)
BPI Mean	4.6 (1.6)	4.5 (1.8)
BPI worst in past week	7.9 (1.9)	7.5 (2.2)
BPI interference	4.5 (2.6)	4.6 (2.3)
BPI – pain interfered with mood	4.4 (3.3)	4.0 (2.9)

Baseline McGill QOL Scores (0 – 10, 10=best quality of life)

	MT mean (SD)	Control mean (SD)
MQOL Overall	6.2 (2.5)	6.3 (2.4)
MQOL Physical well-being	5.3 (2.6)	5.2 (2.4)
MQOL Existential	7.5 (1.7)	7.4 (2.1)
MQOL Support	8.8 (1.7)	8.5 (1.8)

Baseline Memorial Symptom Assessment Scale Scores

(1 – 4, 4=worst symptom distress)

	MT mean (SD)	Control mean (SD)
MSAS Global Distress Index	2.7 (0.6)	2.7 (0.6)
MSAS Physical symptoms	2.7 (0.6)	2.6 (0.6)
MSAS Psychological symptoms	2.6 (0.8)	2.6 (0.8)

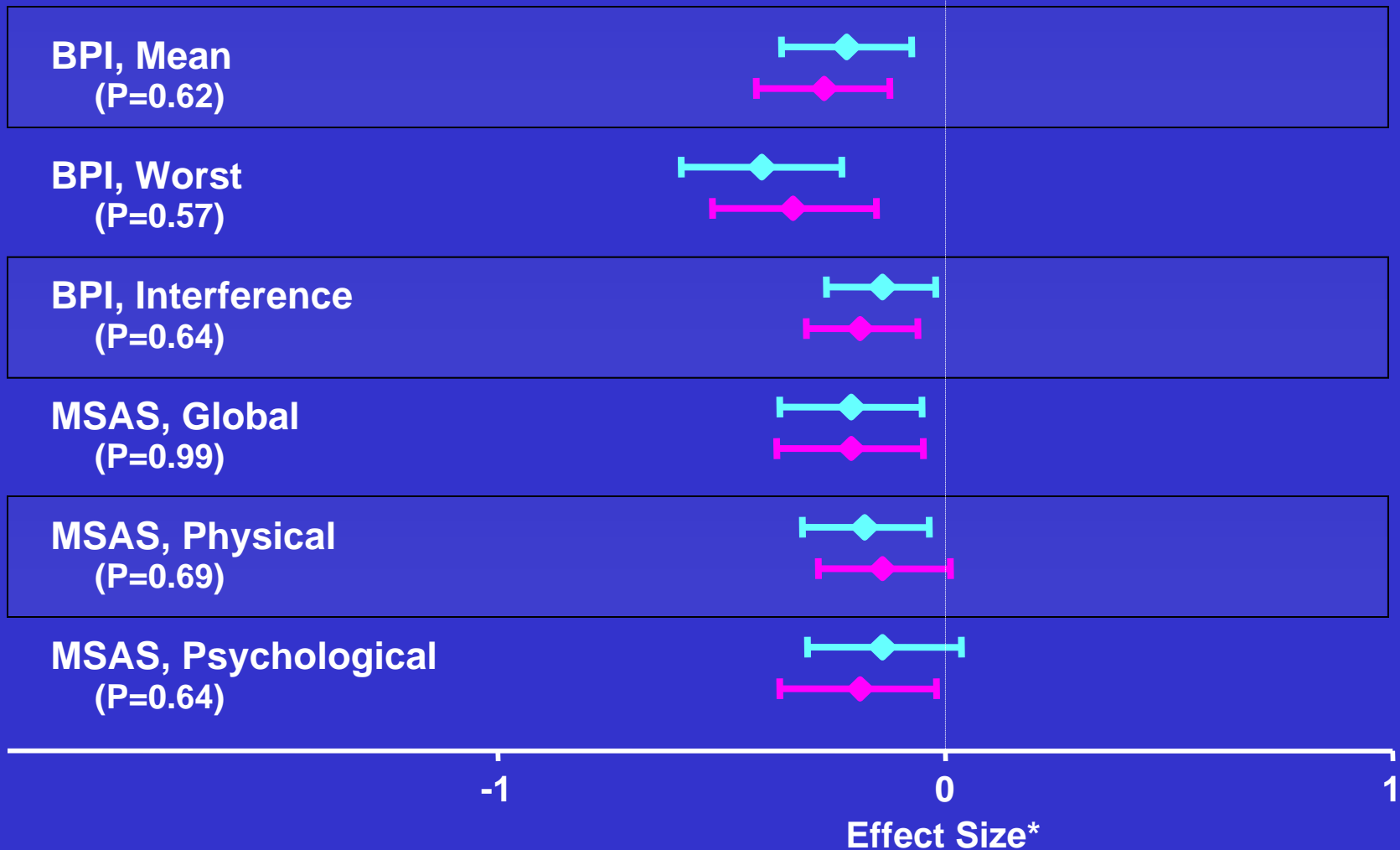


Baseline Total Parenteral Morphine Equivalents in prior 24 hours (mg)

	MT mean (SD)	Control mean (SD)
Total parenteral morphine equivalents in prior 24 hours (mg)	78.9 (125.5)	98.5 (211.4)

No Sustained Effect

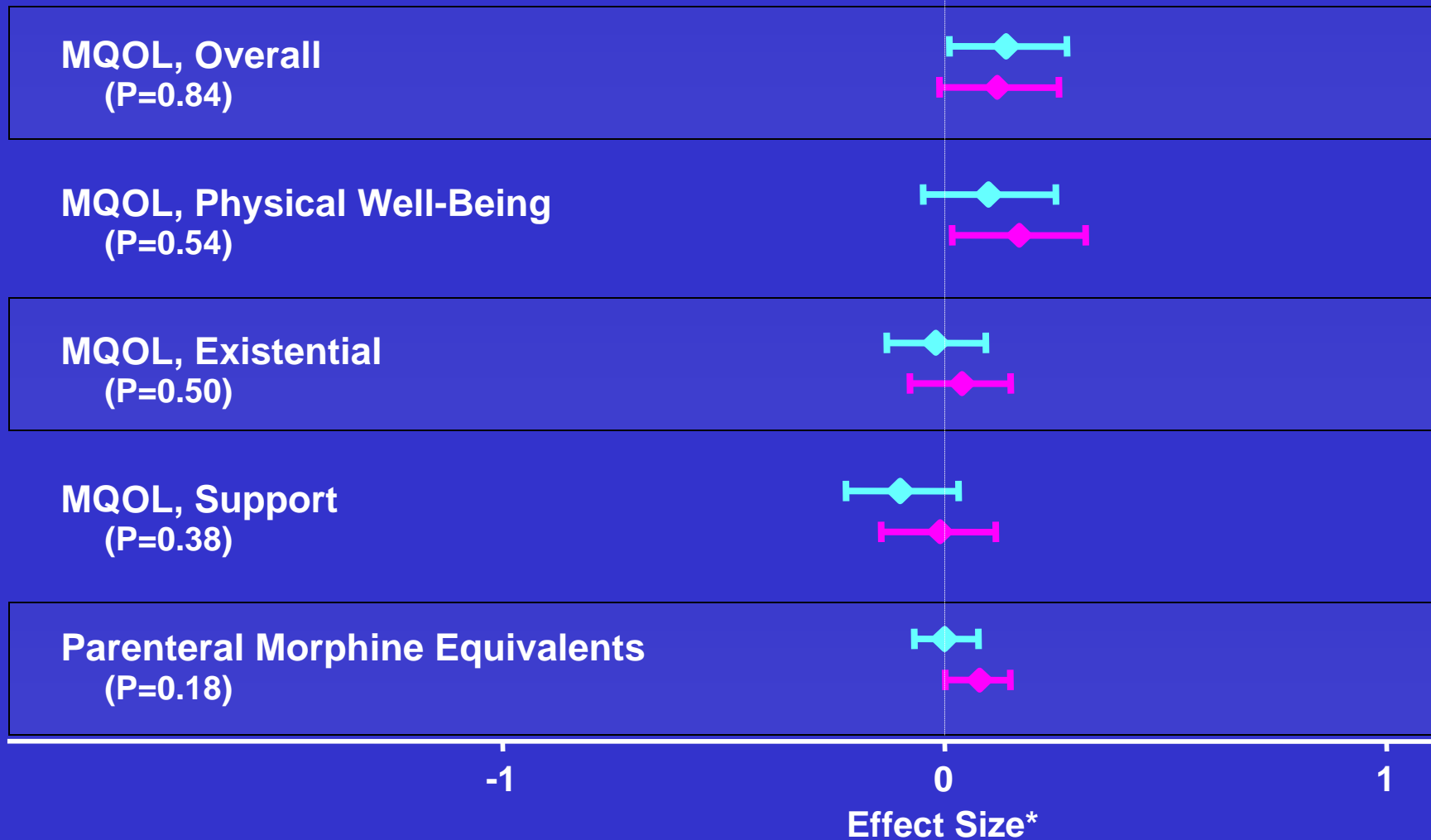
MT (—) vs. Control (—)



*Adjusted for age, comorbid conditions, gender, prior MT, worst pain in prior week, KPS



No Sustained Effect MT (—) vs. Control (—)



*Adjusted for age, comorbid conditions, gender, prior MT, worst pain in prior week, KPS

Summary

- **MT provided greater short-term improvement in pain and mood than did simple touch, findings that were not sustained over time.**
- **Pain scores stable despite NO increase in parenteral morphine equivalents.**
- **No harmful effects of MT identified.**



Limitations

- **Generalizability**
 - Cancer patients only
 - Primarily in the hospice setting
 - Primarily non-Hispanic White
 - Only cognitively intact
 - Trained & experienced massage therapists
- **Sensitivity of outcome measures**
 - “Sustained” effects measured only weekly
 - No measures of sleep
 - May be unmeasured benefits



Strengths

- **Large sample size**
- **Multi-site**
- **Parallel qualitative study – analyses in progress**
- **Multiple measures of primary outcome, pain**



Representative Study Patient Qualitative Quotes

- “I really looked forward to it because it helped me to relax, and the more relaxed the better I felt”
- “I just felt cared for...it felt so nice to have something relaxed related to cancer...rather than injections, it was a nice contrast from that...”
- “...I would sleep better at night which helped a lot...I remember...the feeling of well-being”
- “It was really good...I think at least four hours afterward I had no pain at all”

Conclusions

- **Immediate benefits of MT for pain and mood – evidence supports offering MT on an individual basis and evaluating for immediate beneficial effects.**
- **Improvements in pain, non-pain symptom distress, and quality of life in both study arms may indicate that attention and touch, which are simple and inexpensive to provide, are beneficial to persons with advanced cancer.**

