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Role for Multicomponent Interventions

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Disclosures

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- Stock : None
- Speakers Bureau : None
- Consultant (2 yrs): Astellas (clinical trial design), Vantia (QoL instrument development), Medtronic (non-drug tx for UI)
- Other : Speaker at
  - AUA Foundation Meeting: UI in Primary Care
  - American College of Physicians meeting through an un-restricted educational grant from Astellas

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Outline

1. Significance
2. State-of-the-Art Knowledge
3. Knowledge Gaps and
4. Research Opportunities

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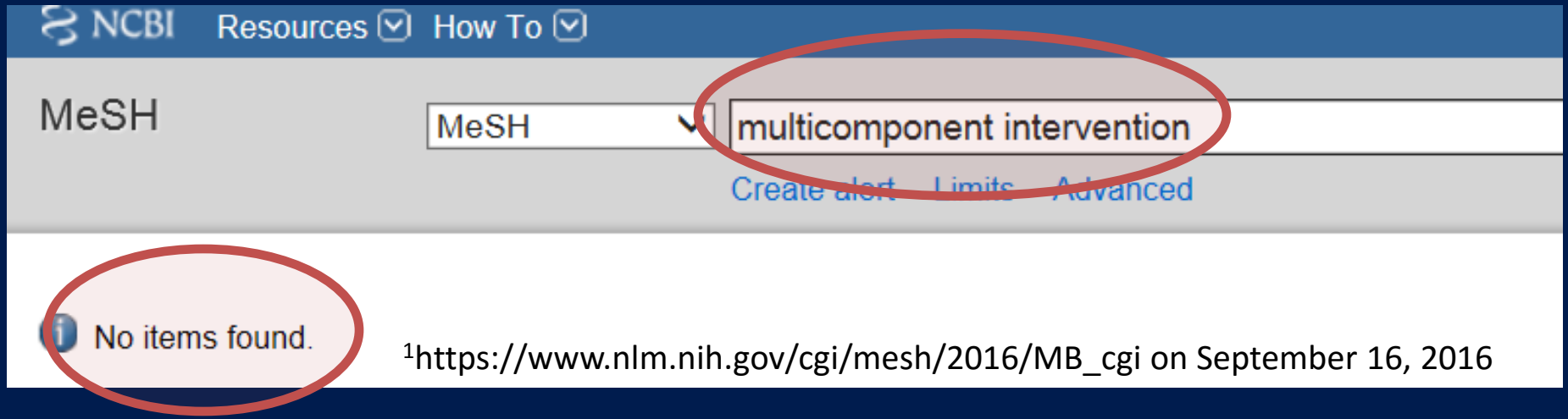
Multicomponent Interventions: Standardized Framework

- Multicomponent Intervention: not a MESH term[1]
- Clinical Trial (Intervention Study) are both MESH terms: . . . in which participants are assigned to receive one or more interventions
- Other modifying terms: *multifaceted*; *complex*; *behavioral plus drug*



[1]https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi on September 16, 2016

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Definitions- AHRQ Focus Group

- Terminology agreement around: Complex, multicomponent, health system interventional trials
- The word multicomponent, by contrast, was generally recommended by the interviewees[1]
  - "*I think, that the value about distinguishing multicomponent interventions are because there are questions about the interaction of the components, which components are critical and variation across the individual components, across different studies. So thinking about them and how to collect information is useful.*"

[1] AHRQ Review, 2014: Systematic Reviews of Complex Multicomponent Health Care Interventions [Internet]. Guise JM, Chang C, Viswanathan M, et al. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Mar.

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Definitions- AHRQ Focus Group

- Terminology agreement around: multicomponent
- The word <u>multicomponent</u>, by contrast, was generally recommended by the interviewees[1]
  - *Interaction of the components*
  - *Which components are critical*
  - *Variation across the individual components*
  - *How that differs across studies*

[1] AHRQ Review, 2014: Systematic Reviews of Complex Multicomponent Health Care Interventions [Internet]. Guise JM, Chang C, Viswanathan M, et al. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Mar.

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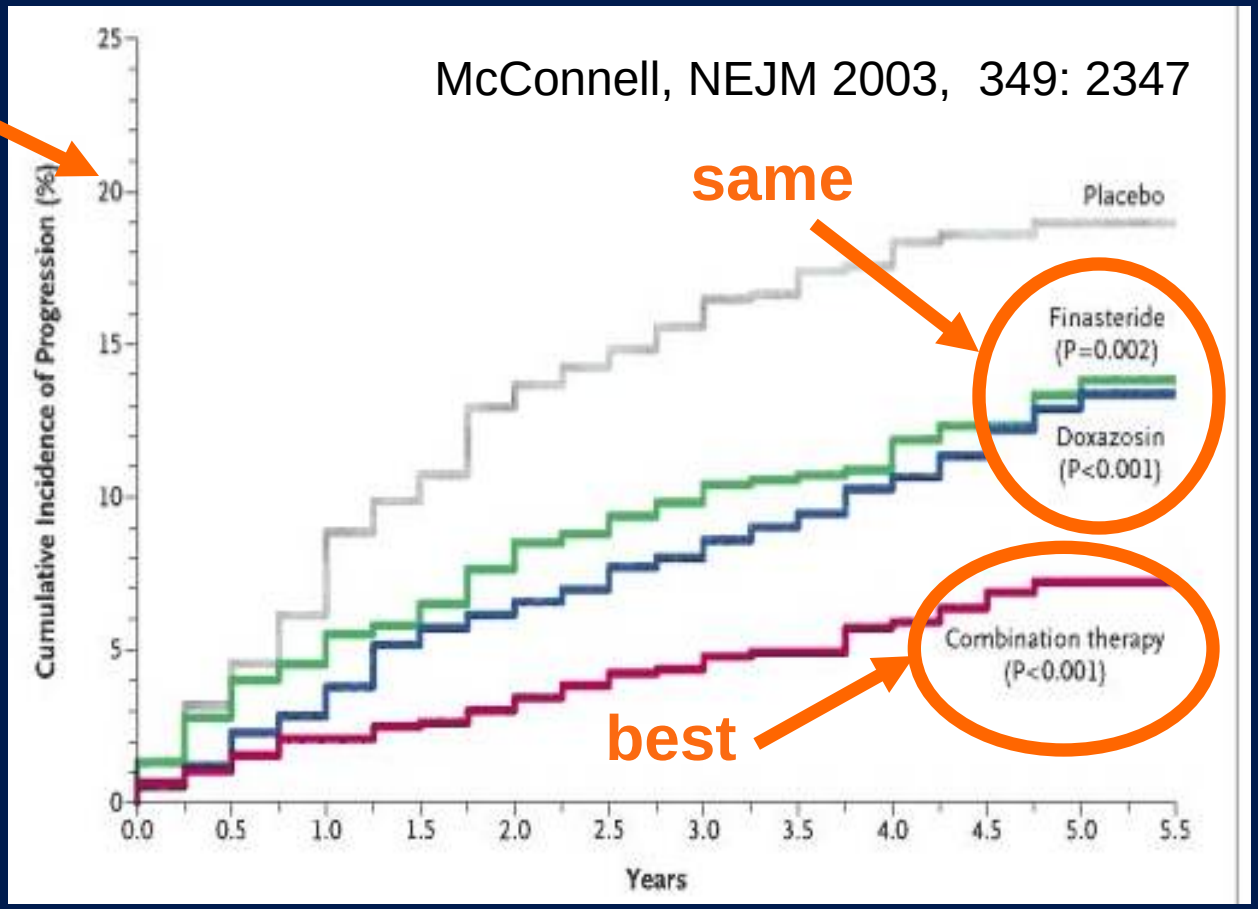
MTOPS (α-blocker + 5-αRI) for BPH sx's: a multicomponent intervention?

Lower progression better



Must the interventions come from different domains? 3 or more? Include behavioral?

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State-of-the-Art Knowledge

- Multicomponent interventions common
  - Smoking cessation, asthma management, reducing buzzed-driving, weight loss, HIV elimination
- Conditions with multiple, interacting risk factors
  - Geriatric conditions specifically- falls, delirium, functional dependence, urinary incontinence[1], insomnia[2]
- Multicomponent interventions for achieving multiple outcomes

[1]Burgio et al. JAGS 2011, [2]Tyagi JAGS 2014

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State of Art Knowledge: Role for Multicomponent Interventions

- Conditions with multiple, interacting risk factors
- Where single intervention less effective/ineffective: delirium
  - No clear evidence on cholinesterase inhibitors, antipsychotic medication or melatonin to reduce incidence
  - Strong evidence supporting multi-component interventions to prevent delirium in hospitalised patients[1]
- Targeting multiple outcomes[2]

[1]Siddiqi et al. Dementia and Cognitive Improvement Group. 2016

[2]Wenger et al. Primary Care intervention for Falls, UI, Dementia. 2009

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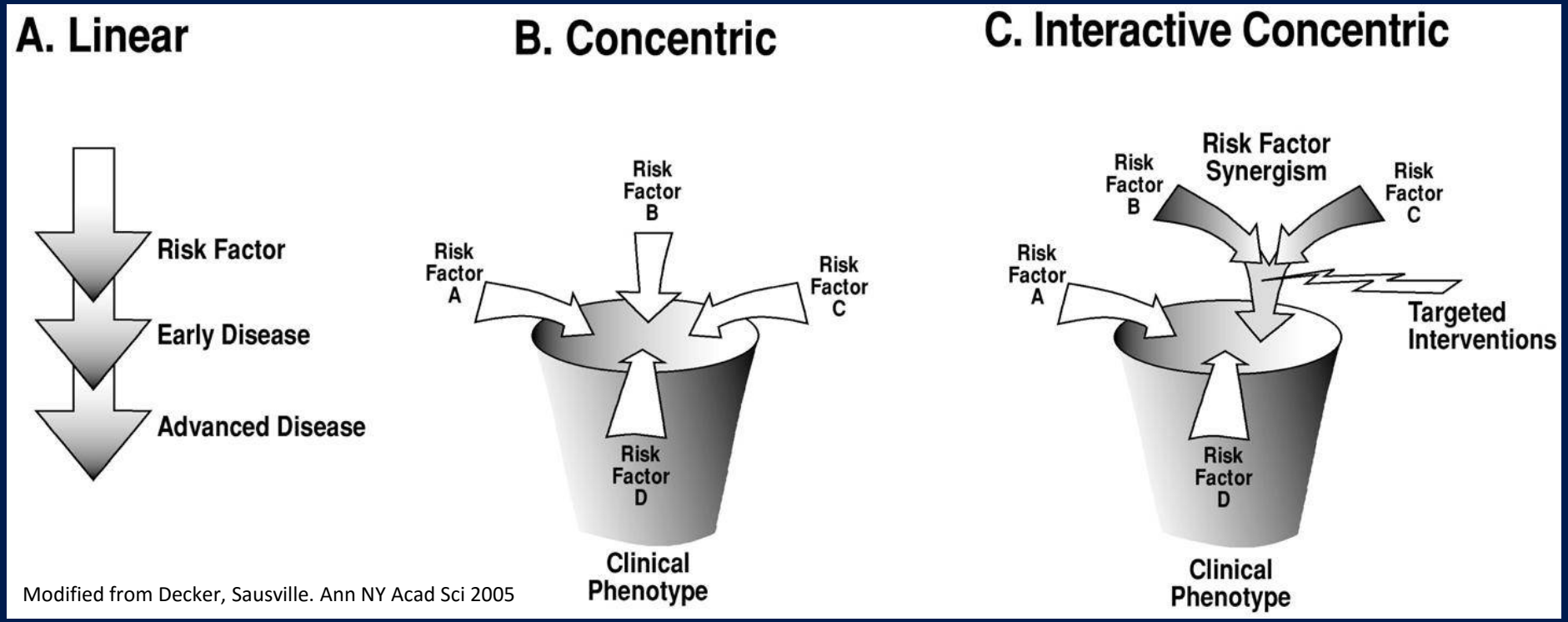
State of the Art Knowledge: Multiple Interacting Risk Factors



Modified from Decker, Sausville. Ann NY Acad Sci 2005

In Inouye, Studenski, Tinetti, Kuchel. J Amer Geriatr Soc 2007

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Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept

Hypertension →

Congestive Heart Failure →

Symptomatic Congestive Heart Failure with Nocturia

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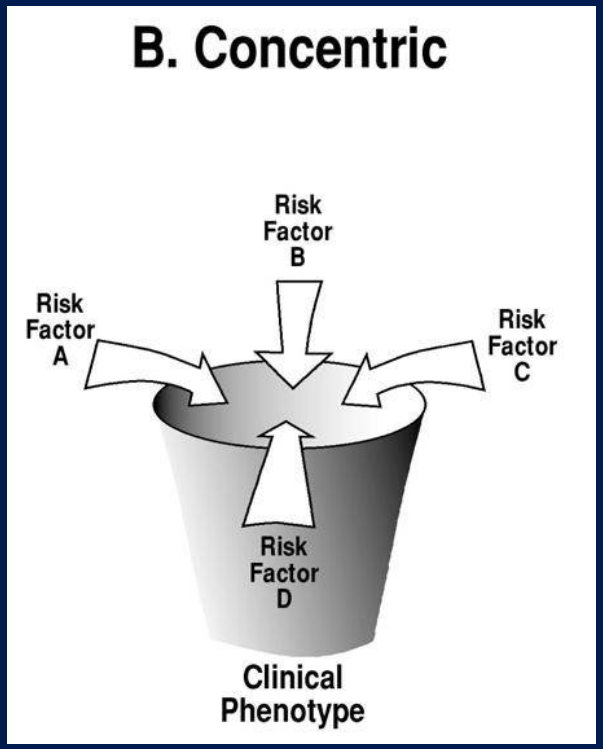
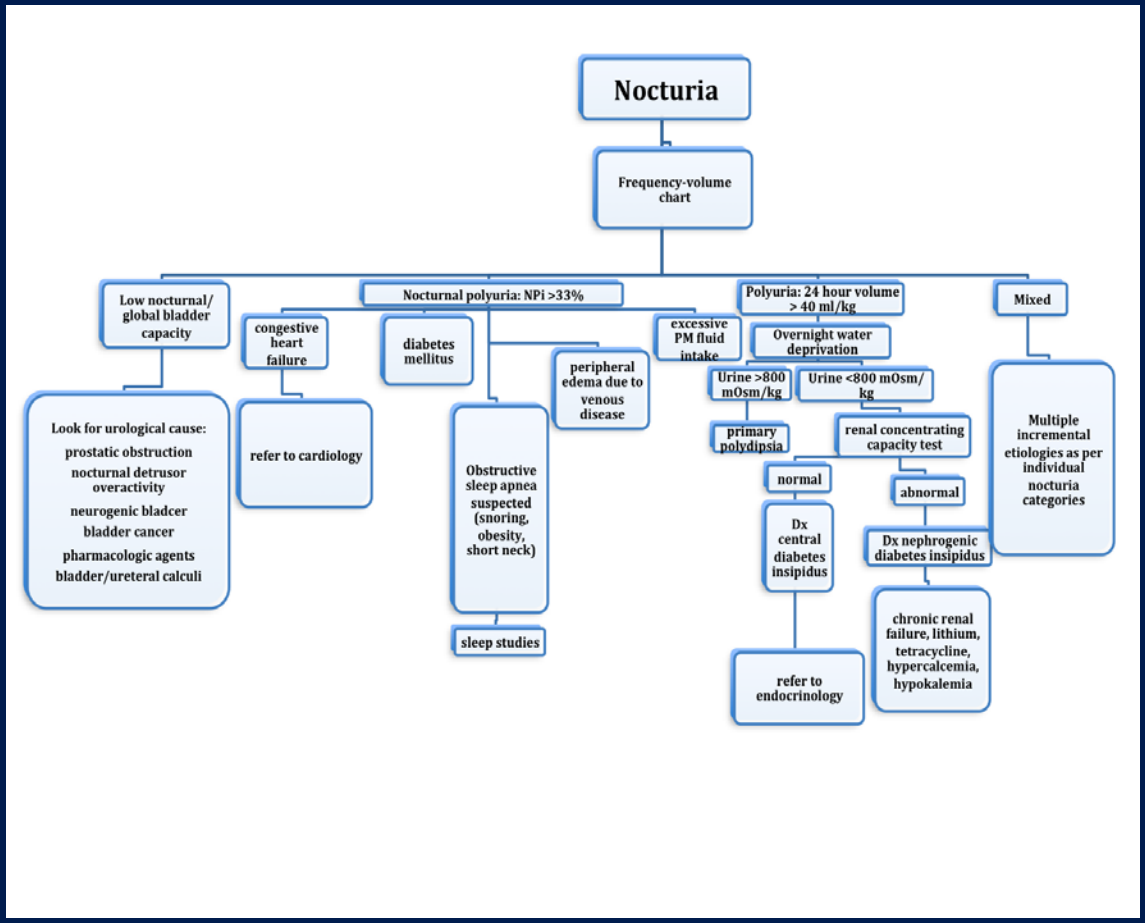
Geriatric Syndromes: Clinical, Research and Policy Implications of a Core Geriatric Concept





Weiss, Blaivas, et al. BJU Int. 2013

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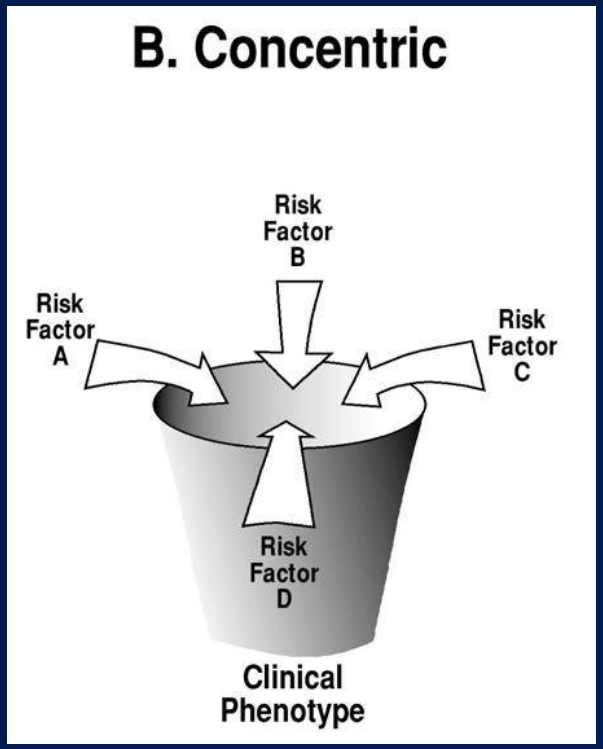

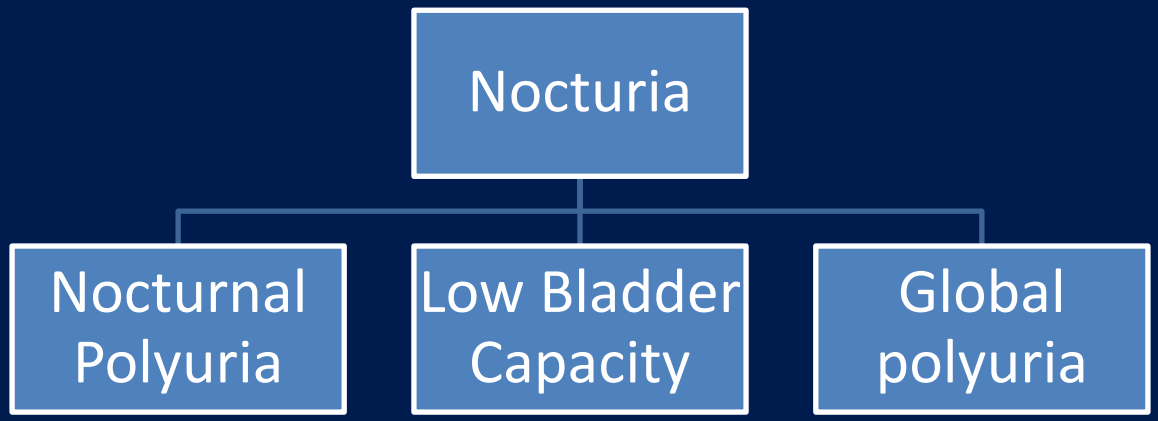

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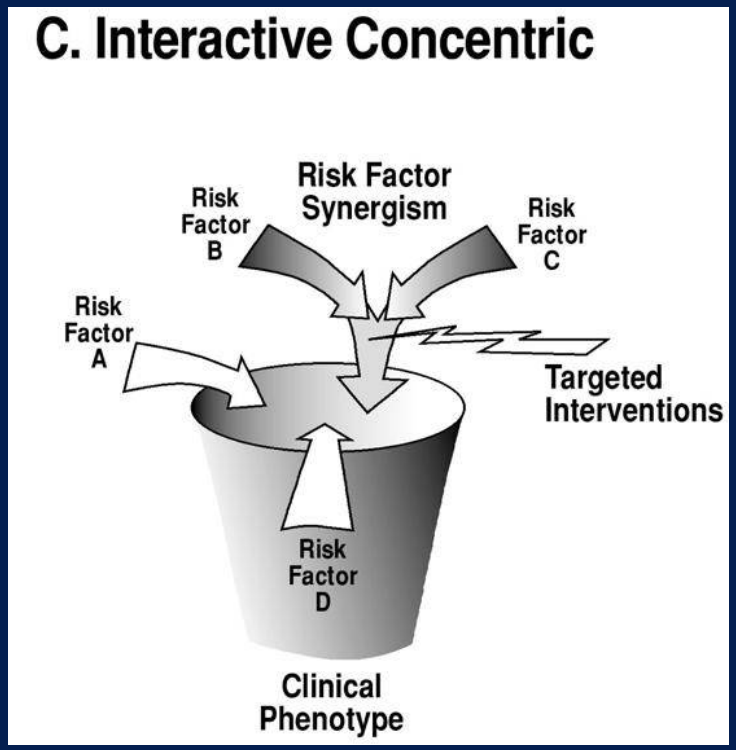

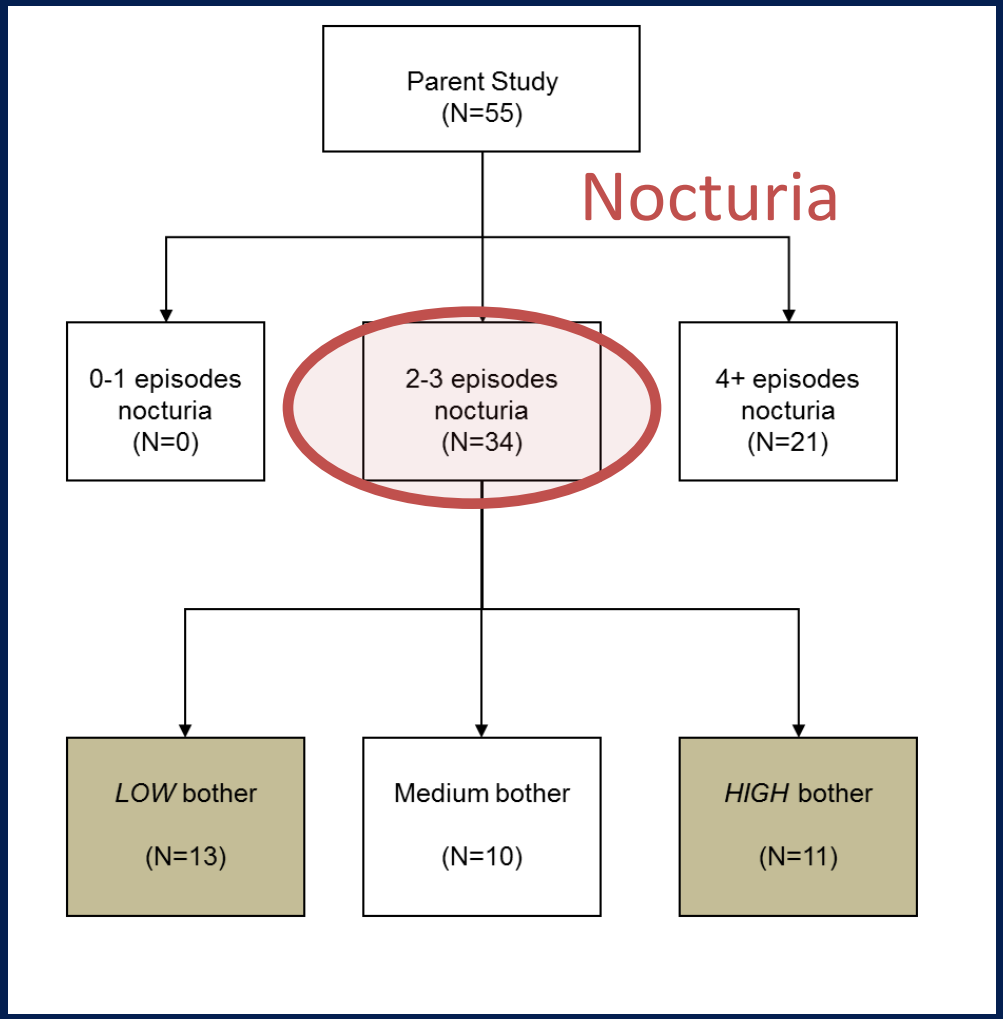

Vaughan, Eisenstein, Bliwise, Endeshaw, Nagamia, Wolf, Johnson. Int J Clinical Practice 2012

Interaction between voiding and sleep → *bother from nocturia*

Sleep Characteristic	*LOW* Bother (±s.d.)	*HIGH* bother (±s.d.)	*P*-value
Return to sleep (min)	16.1 (± 11.4)	28.8 (± 13.9)	0.03
Fatigue- Morning	5.7 (±0.9)	4.7 (±0.7)	0.01

Higher # better

Vaughan, Eisenstein, Bliwise, Endeshaw, Nagamia, Wolf, Johnson. Int J Clinical Practice 2012

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SOTA: Where Single Interventions Less Successful

The New England Journal of Medicine

Volume 331 SEPTEMBER 29, 1994 Number 13

A MULTIFACTORIAL INTERVENTION TO REDUCE THE RISK OF FALLING AMONG ELDERLY PEOPLE LIVING IN THE COMMUNITY

Mary E. Tinetti, M.D., Dorothy I. Baker, Ph.D., R.N., C.S., Gail McAvay, M.S., Elizabeth B. Claus, Ph.D., Patricia Garrett, M.H.S., R.N.-C., Margaret Gottschalk, P.T., Marie L. Koch, M.S., P.T., Kathryn Trainor, M.S., and Ralph I. Horwitz, M.D.

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Experimental Designs[1]

- Test multicomponent interventions for multifactorial health conditions
- Identification and selection of modifiable risk factors related to the outcome of interest
  - Known risks → targeted risk factors (foot problems[2], palmomental reflex[2], sedative use[2,3], polypharmacy[3]), hearing loss
- Selection of intervention components to reduce the deleterious effects of the modifiable risk factors

[1]Allore et al. Clinical Trials 2005; [2]Tinetti NEJM 1988, [3]Tinetti NEJM 1994

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Elements of Multicomponent Trials

Table 1 Elements of the nine illustrative multicomponent intervention trials

Author, year (location)	Tinetti *et al.* 1994 [8] (USA)	Inouye *et al.* 1999 [7] (USA)	Beyth *et al.* 2000 [17] (USA)	Counsell *et al.* 2000 [14] (USA)	van Haastregt *et al.* 2000 [15] (Netherlands)	Strandberg *et al.* 2001 [10] (Finland)	Timonen *et al.* 2002 [18] (Finland)	Jensen *et al.* 2003 [16] (Sweden)	Shaw *et al.* 2003 [9] (UK)
Outcome	Falls	Delirium	Warfarin-related bleeding	Functional decline	Falls and impaired mobility	Cardiovascular disease	Strength, balance and mobility	Falls and injury	Falls and injury
Prevalence of risk factors	Yes	Yes	Not reported	Not reported	Not reported	Yes	Not reported	Not reported	Yes
Correlation among risk factors	Correct for in analysis	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Were risk factors grouped?	Yes	Yes	Apparently	Difficult to determine	Difficult to determine	Difficult to determine	Difficult to determine	Difficult to determine	Yes
No. of intervention components	8	7	2	Difficult to determine	Difficult to determine	8	Difficult to determine	7	4
Measurement of predetermined risk factors at follow-up	Yes	Yes	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Yes
Eligibility	Broad	Restrictive	Restrictive	Broad	Broad	Broad	Restrictive	Broad	Restrictive
Treatment assignment	Randomized by physician	Matched	Stratified randomization by subject	Randomized by subject	Randomized by subject	Randomized by subject	Randomized by subject	Randomized by facility	Stratified randomization by subject
Blinded allocation and assessment	Blinded allocation and assessment	Blinded assessment	Blinded allocation and assessment	Blinded allocation and assessment	Blinded allocation	Blinded allocation and assessment	Blinded allocation	Blinded allocation	Blinded allocation and assessment
Sample size or power	Not provided	Not provided	Provided	Provided	Provided	Provided	Not provided	Provided	Provided
Assignment of components	Standardly tailored	Standardly tailored per protocol assessed daily	Participants received all components	Standardly tailored	Standardly tailored	Standardly tailored	Participants received all components	Standardly tailored	Standardly tailored
Estimated component effects	Effect of risk factor reduction	Effect of risk factor reduction	No	No	No	No	No	No	Effect of risk factor reduction

Allore, Tinetti, Gill, Peduzzi. Experimental designs for multicomponent interventions among persons with multifactorial geriatric syndromes. Clinical Trials. 2005

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Outcome									
Prevalence of risk factors									
Correlation among risk factors									
Were risk factors grouped?									
No. of intervention components									
Measurement of predetermined risk factors at follow-up									
Eligibility									
Treatment assignment									
Blinded allocation and assessment									
Sample size or power									
Assignment of components									
Estimated component effects									

- Outcome
- Risk factor prevalence & correlation
- # components and assignment
- Measurement of risk factors at follow-up
- Blinded allocation and assessment
- Sample size and power
- Estimated component effects

Allore, Tinetti, Gill, Peduzzi. Experimental designs for multicomponent interventions among persons with multifactorial geriatric syndromes. Clinical Trials. 2005

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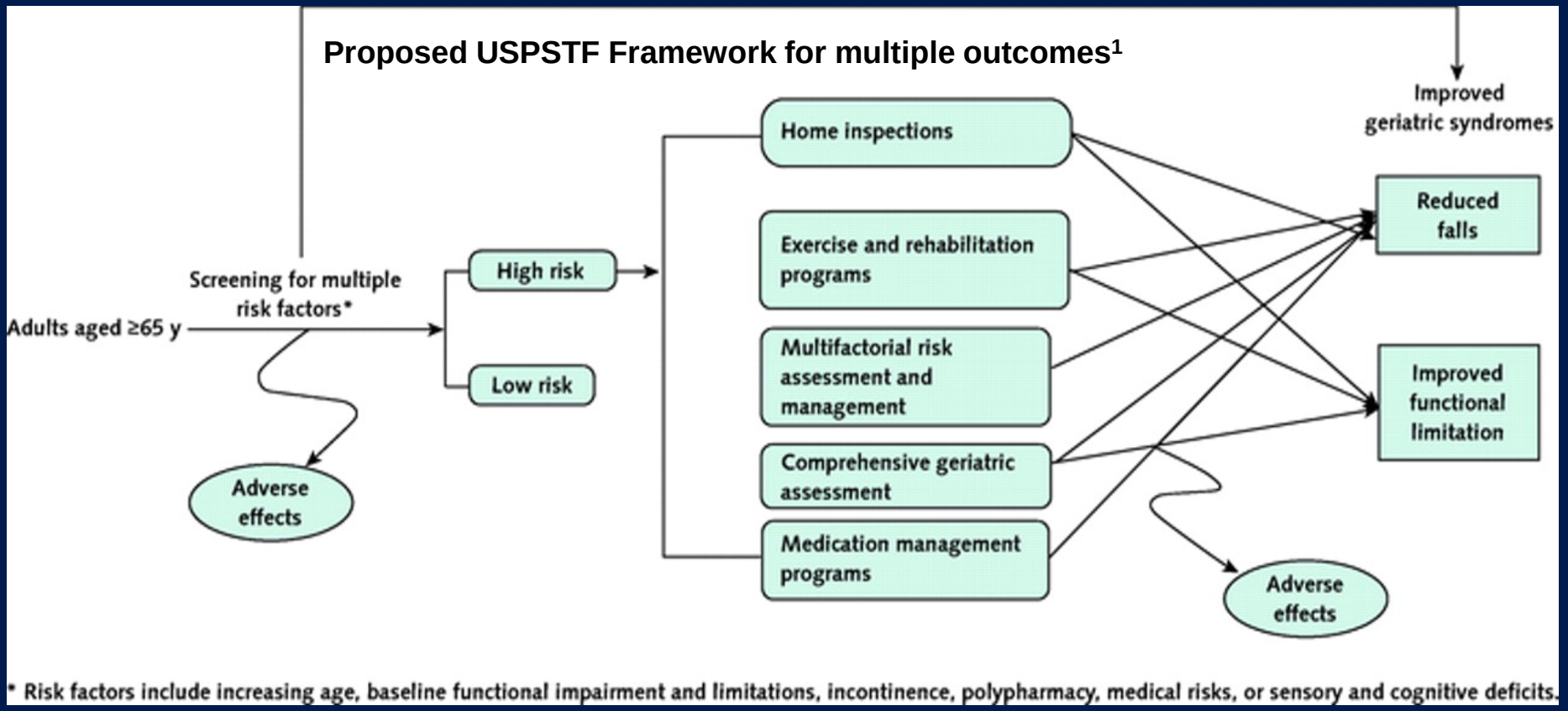
Targeting of Multiple Outcomes with Multiple Interventions



[1] Leipzig R M et al. Ann Intern Med 2010;153:809-814;

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Knowledge Gaps

- Standardized definition, MESH term
- Methodological concerns about meta-analyses of multicomponent trials
- Which elements belong?
- How multicomponent strategies fit together (macro)- National strategy for HIV; Alzheimer's disease

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Combined Multicomponent: Vision; Goals; Indicators

Goals of the National HIV Strategy

1. **Reduce New Infections**
2. **Increase Access to Care and Improve Health Outcomes for People Living with HIV**
3. **Reduce HIV-Related Health Disparities and Health Inequities**
4. **Achieve a More Coordinated National Response to the HIV Epidemic**

https://www.aids.gov/federal-resources/national-hiv-aids-strategy/nhas-update.pdf

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Goals → Steps: Multicomponent Interventions

STEP 1.B		Expand efforts to prevent HIV infection using a combination of effective, evidence-based approaches.
1.B.**1**		Design and evaluate innovative prevention strategies and combination approaches for preventing HIV infection in high-risk populations and communities, and prioritize and promote research to fill gaps in HIV prevention science among the highest risk populations and communities.
1.B.**2**		Support and strengthen integrated and patient-centered HIV and related screening (sexually transmitted infections [STI], substance use, mental health, intimate partner violence [IPV], viral hepatitis infections) and linkage to basic services (housing, education, employment).
1.B.**3**		Expand access to effective prevention services, including pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP).
1.B.**4**		Expand prevention with persons living with HIV.

https://www.aids.gov/federal-resources/national-hiv-aids-strategy/nhas-update.pdf

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Meta-analysis Consideration- AHRQ Framework (9 points)

- Holistic- look at effectiveness of whole bundle
- Intervention features or factors- group by components (exercise + PT); active components (home monitoring); theory; context
  - PICOTS framework (Patient population, Intervention, Comparator, Outcomes, Timing, Setting); they focus on ways of categorizing the intervention or its components, the setting, or both.
- Factors influencing success or behavior- realistic (evidence informed care), mechanism of action, configurational (needed, but not sufficient)

AHRQ Review, 2014: Systematic Reviews of Complex Multicomponent Health Care Interventions [Internet]. Guise JM, Chang C, Viswanathan M, et al. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Mar.

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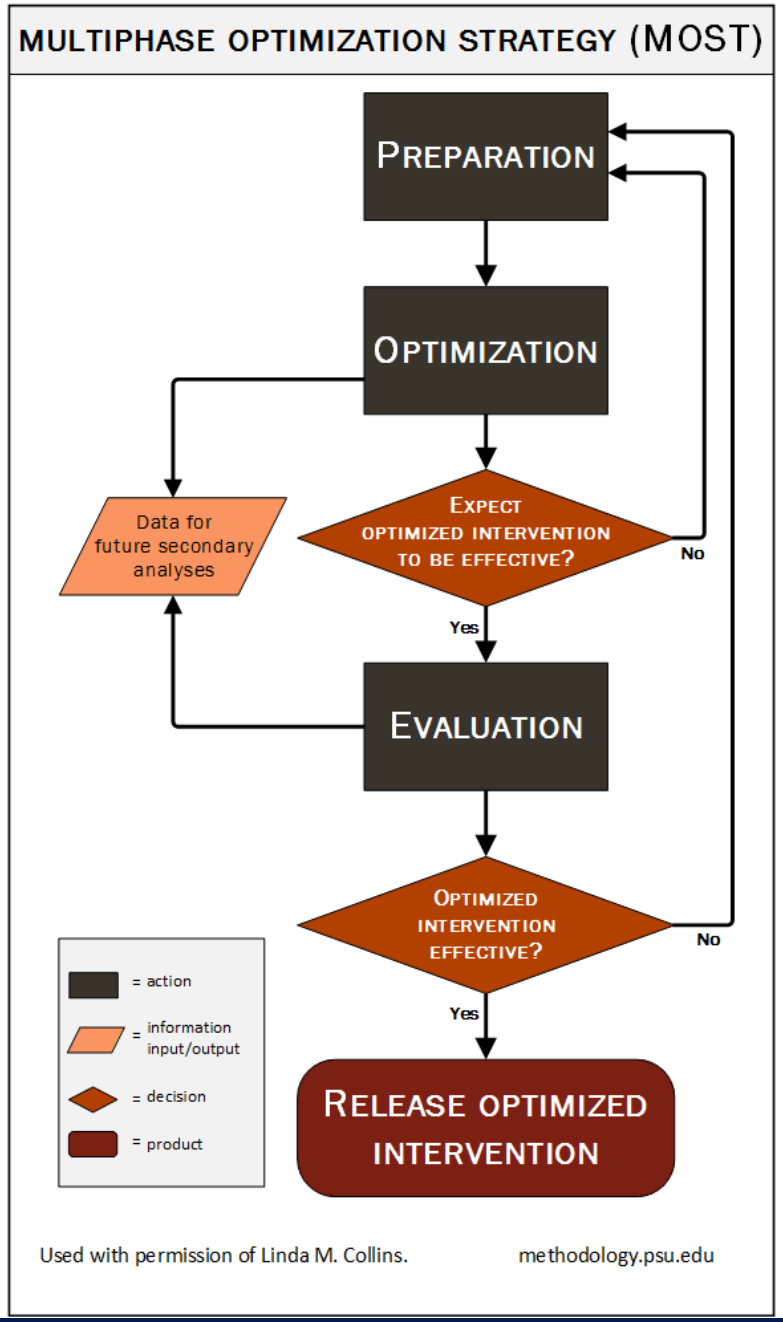
Choosing Multicomponent Elements

- Multiphase optimization strategy (MOST)
- Sequential experimentation with results feeding forward
- Calculated risks for speed
- Move intervention science fastest, even if slower progress in the short run
- Standardized RCT only following optimization

Figure 1.



Collins, L. M., et al. (2011). *Annals of Behavioral Medicine, 41,* 208-226.

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Research Opportunities

- MESH heading, standards
- Look at AlzDz and HIV models for overarching strategy for progress as potential model
- Collaborative efforts with behavioral scientists, implementation science
- Packaging UI/LUTS outcome measures to be integrated into other trials
  - SPRINT, LIFE, SOF

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Future Research Framework[1]

Table 3 Areas for future research and questions and issues to be addressed

Areas for research	Unanswered questions and issues
Reporting of multicomponent intervention trials	Develop a common terminology for the elements of multicomponent intervention trials. Develop reporting standards.
Study design	Can full or fractional factorial designs be applied to multifactorial geriatric syndromes and what are their limitations?
Selection of modifiable risk factors	How many risk factors can be studied in a single trial? What is the minimum prevalence of a risk factor? What is an acceptable level of correlation among risk factors? How can risk factors be grouped?
Selection and assignment of intervention components	How many components can be studied in a trial? How to determine which risk factors an intervention may affect? How to best assign components to participants in a trial? By how much does a component need to reduce the risk of the targeted risk factor to be effective? How can high adherence with component assignment be achieved?
Sample size determination	How to determine the sample size needed to estimate component effects? How to extend sample size determination for clustered and other types of designs?
Estimation of component effects	What is the appropriate comparison group? What methods will provide unbiased estimates of individual component effects?

[1]Allore et al. Clinical Trials 2005

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Future Research Framework[1]

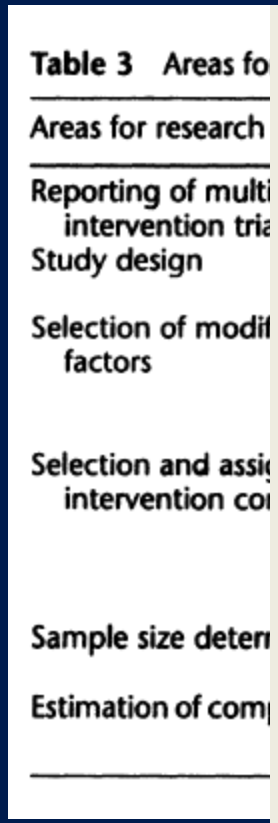
Table 3 Areas fo

Areas for research

Reporting of multi intervention tria

Study design

Selection of modif factors

Selection and assig intervention co

Sample size deter

Estimation of com

- Terminology, reporting standards
- Design issues
- Ideal # risk factors, correlation, grouping
- How many components, assignment
- Sample size, comparison group
- Effect of individual components, bundle of components

[1]Allore et al. Clinical Trials 2005

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Recap: Multicomponent Interventions

1. Significance
2. State-of-the-Art Knowledge
3. Knowledge Gaps and
4. Research Opportunities