

# Issues in Randomized Clinical Trials Involving Behavioral Interventions

Module V: Management and Administrative Issues

## *Trial Organization and Monitoring Issues*

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U.S. Department of  
Health and Human  
Services



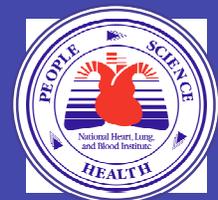
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# ***Trial Organization and Monitoring Issues***

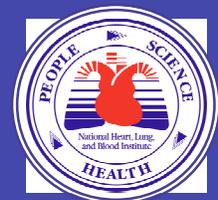
- **Mechanisms of funding & role of NIH program staff**
- **Trial organization & functioning**
- **Quality control, monitoring, & oversight**



# Mechanisms of funding & role of NIH program staff

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- Mechanisms of funding (general)
- Investigator-initiated applications
  - examples, role of staff
- RFA for individual studies
  - examples, role of staff
- RFA/RFP for multicenter studies
  - example, role of staff



# Mechanisms of Funding (1)

- **Investigator-initiated Applications**
  - Topic of the investigator's choosing
  - 80% of NIH funding
  - Due dates 3/year (Feb, June, Oct)
  - Usually for single center studies
  - Can be for multi-center studies
- **Program Announcements**
  - To encourage applications in an identified area
  - Standard due dates 3/yr
  - Generally no set-aside funding
  - Peer reviewed as investigator-initiated



# Mechanisms of Funding (2)

- **Request for Applications (RFA)**
  - For grants in a specified topic area
  - Can be for individual, single-center studies or for multi-center studies (cooperative agreements)
- **Request for Proposals (RFP)**
  - For contracts
  - Often for multi-center studies
- **Both RFAs and RFPs**
  - Set-aside funding
  - Due dates individualized
  - Special review group



# Investigator-Initiated Behavioral RCTs: Examples

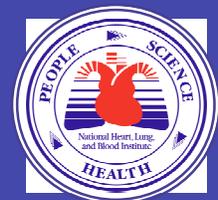
- **Meditation** for High Blood Pressure (*Lane*)
  - RCT testing effects of meditation vs progressive relaxation vs usual care on blood pressure
- **Stress** reduction & CVD morbidity & mortality in blacks (*Schneider*)
  - RCT testing effect of TM on combined CVD morbidity and mortality events
- **Prevention of overweight** in preschool minority children (*Fitzgibbon*)
  - Randomized trial of Head Start sites serving Black and Hispanic populations to test a diet and physical activity intervention
- **Increasing physical activity** in low-income women (*King*)
  - Randomized trial of adult education classes testing physical activity intervention for women



# Role of Program Staff in Investigator-initiated grants

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- Advise applicant **prior to submission** (convey policies and procedures, advise on scientific matters)
- Advise applicant **after peer review** (assess likelihood of funding, resubmission)
- Monitor **recruitment** progress
- Monitor progress **annually** and as needed
- Advise PI on **needs that arise** (e.g., requests for administrative supplement)



# When to Develop an Initiative (PA, RFA, RFP)

- To stimulate investigator-initiated activity in a certain topic area (example: adherence research)
- When a multi-center study is needed to address an important research question (example: obesity prevention in American Indians)



# Initiatives for Single vs Multi-center Studies

- Depends on the “stage of research” – need to know the literature
- If little prior research on a topic area, or research questions can be answered with smaller sample size, multiple smaller studies are justified
- Multi-center study may be needed to achieve sufficient sample size for power (e.g., event trial), multiple sites for generalizability
- Single or multi-center studies can test either efficacy or effectiveness questions



# RFA for Single-center Studies

## *Example: Adherence RFA*

- “Overcoming **barriers to treatment adherence** in minorities and persons living in poverty”
- To test innovative practical **interventions** in clinical & community settings **to improve adherence** in minorities and low SES
- Stage of research indicated multiple smaller studies needed
- RFA-HL-01-005 released Jan. 2001



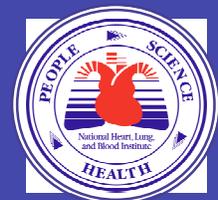
# Adherence RFA Funding & Structure

- 13 grants funded in September 2001:
  - 11 funded by NHLBI  
(5 with funds from National Center for Minority Health and Health Disparities)
  - 2 funded by NCI
- Each study is independent
- Investigators meet annually



# Adherence RFA: Funded Projects on HTN

- **Patient-Physician Partnership** to Improve HTN Adherence (*L Cooper, John Hopkins Univ*)
- **New Strategies to Enhance Drug Adherence** in HTN (*R DeBusk, Stanford Univ*)
- **Interactive Multirisk-Factor** Intervention for HTN Blacks (*R Friedman, Boston Med Center*)
- **HTN and Adherence in Rural Practice** (*P Greene, Univ. AL @ Birmingham*)
- **Improving Medication Use** in Patients with HTN (*M Murray, Indiana Univ*)
- **Motivational Interviewing** in HTN African Americans (*G Ogedegbe, Cornell Univ*)
- **Adherence to Weight Loss** for HTN in AA Women (*T Lasatar, Brown Univ*)



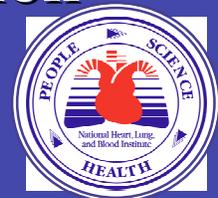
# Adherence RFA: Funded Projects on Other Topics

- **Lifestyle** Adherence in High CVD Risk African-Americans (*D Hyman, Baylor College of Medicine*)
- Does Shared Decision-Making Improve Adherence in **Asthma**? (*S Wilson, Palo Alto Medical Foundation*)
- Reducing Barriers to **Pediatric Asthma** Treatment Adherence (*D Drotar, Case Western Reserve University*)
- Chinese Community **Smoking Cessation** Project (*C Wong, Univ CA at San Francisco*)
- Treatment of **Nicotine Dependence** Among HTNs (*D Wetter, UT M.D. Anderson Cancer Center*)
- Improving Patient Adherence to **Cancer Treatment** (*K Ell, Univ Southern California*)



# Role of Program Staff in Standard RFAs

- **Develop RFA** based on literature and recommendations, e.g., from advisory groups
- Work with review staff on **peer review** plans
- Develop **program plan** after review identifying applications to fund
- **Monitor** as for investigator-initiated grants
- Establish **communications** between investigators, e.g., annual meetings, interim conference calls, websites, listserves
- Plan for **collaborative** publications, dissemination



# Multicenter Studies: RFA vs RFP

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- **Advantages of RFAs:**
  - Funding process is simpler (no negotiations)
  - Does not require OMB clearance for measurement instruments
- **Advantages of RFPs:**
  - More control by program staff of budget and research design
  - Products are “deliverables” to the IC (e.g., datasets, intervention materials)



# Coop Agrmt RFA for Multi-center RCT

## *Example: Pathways*

- “Obesity Prevention in American Indians/Alaska Natives”
- To test school-based interventions focused on primary prevention of obesity in AI/AN 3rd-5<sup>th</sup> graders
- RFA NIH-92-HL-08-P released in 1992
- Sample size needed required multiple sites; 4 field centers and one coordinating center funded 1993-2003



# Pathways Study Aims

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- **Primary aim:**

To evaluate a comprehensive, culturally appropriate program for the primary prevention of obesity in Native American school-age children (% body fat primary outcome)

- **Secondary aims:**

To evaluate the impact of the intervention on physical activity; dietary fat; and knowledge, attitudes & behaviors related to food choices and physical activity



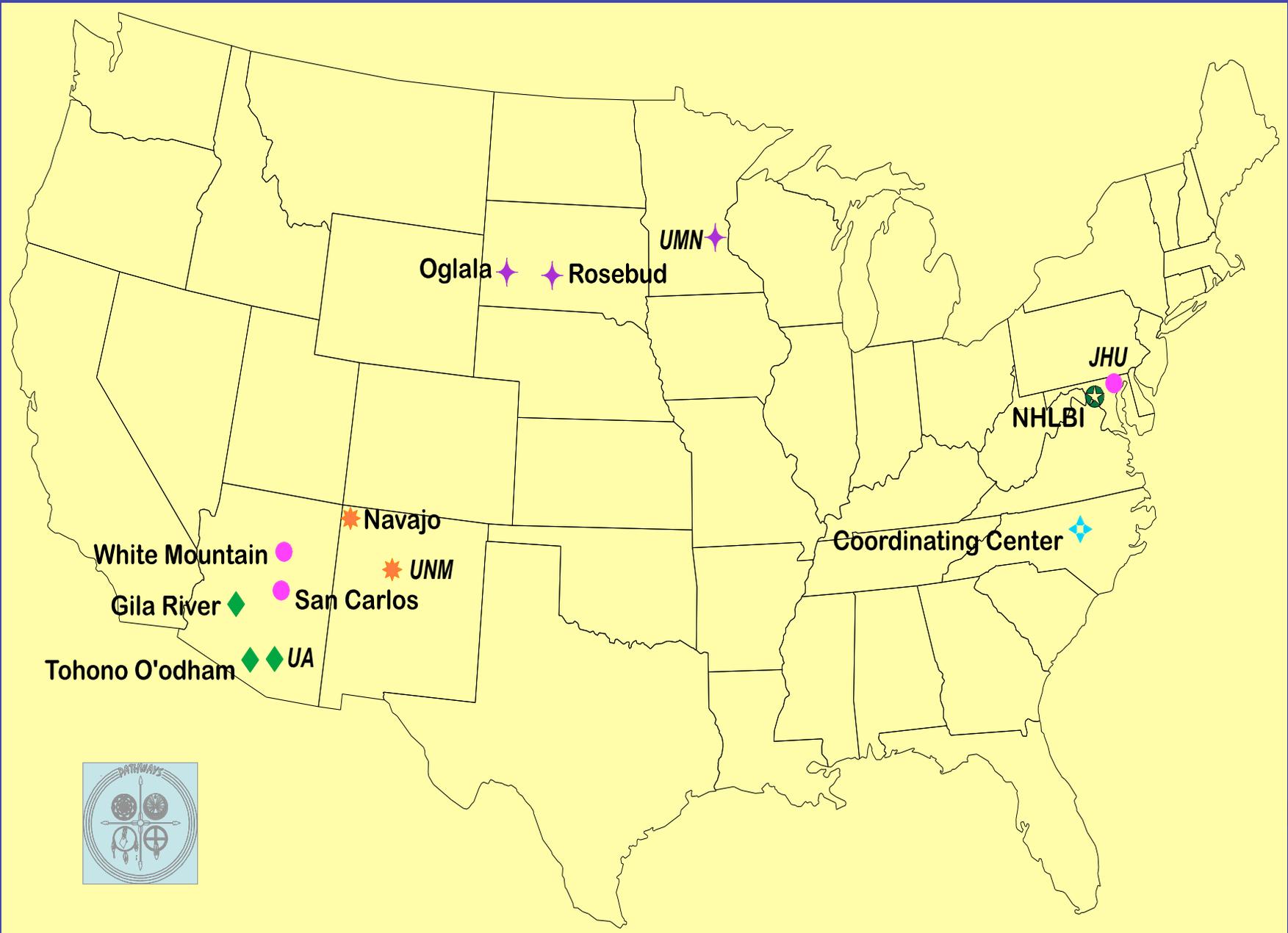
# Pathways Partnerships

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- 5 universities
- 7 Indian nations
- 41 schools
- 1,704 American Indian 3<sup>rd</sup> graders
- NHLBI



# Pathways Sites



# Pathways Design

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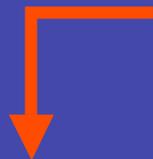
41 schools in 4 Field centers



Baseline measurements



Randomization  
of schools



Intervention



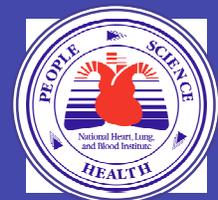
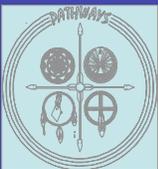
Control



# Pathways Approvals

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- NHLBI Protocol Review Committee and DSMB
- Tribal councils and review boards
- University Institutional Review Boards (IRBs)
- School boards
- Parental written permission
- Child written / verbal consent



# Pathways Intervention

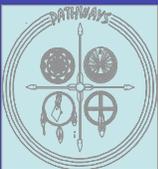
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- **Components**

- Health promotion curriculum, grades 3-5
- Family involvement
- School meal program
- Physical activity programs (PE, recess, classroom)

- **Foundation**

- Social Learning Theory
- American Indian cultural concepts & traditions



# Pathways Summary of Results

- Lowered the % fat in school meals.
- Students reported higher physical activity, but no difference in objective measures.
- Substantial increases in % BF over 3-yrs in intervention and control groups – no difference between groups



# Role of Project Officer in Multi-center Studies (coop agrmts or contracts)

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- **Oversight of entire project**
- **Substantive involvement in all aspects of the study**
  - Protocol development
  - Design of study components and procedures
  - Quality control and monitoring
  - Analysis and reporting
- **Manage overall budget**
  - Fairness across sites
  - Total within approved allocation
- **Assure attention to procedures**
  - Proper oversight, e.g., DSMB
  - Approvals needed
  - NIH/IC policies

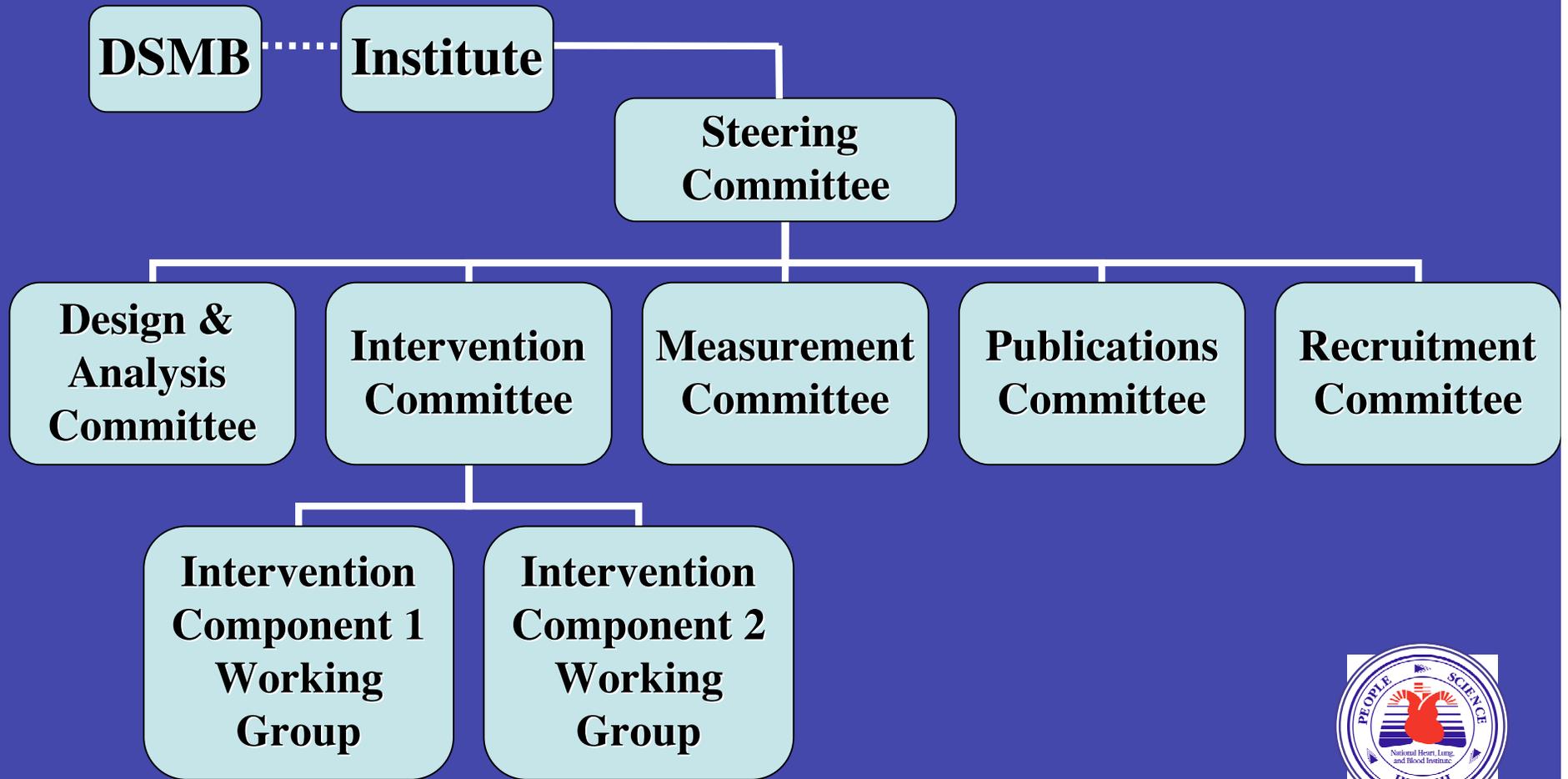


# Trial Organization & Functioning

Focus on multi-center studies



# Typical Multi-center Study Organizational Structure



# Organizational Issues

- **RFA/RFP** sets out the basic study aims; investigators and IC collaborate to develop the protocol and manual of procedures
- **Steering Committee**, governing body of study, made up of PIs & PO – generally each site has one vote
- All funded sites represented on all **committees**
- Selection of **committee chairs** important!
- May need “**Executive**” **Committee** – important to do this at outset, later addition of Exec committee not well received



# Setting the Stage with the Investigators

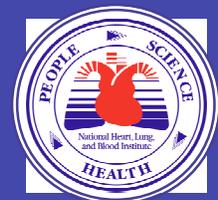
- RFA/RFP and first SC meeting set stage for **collaboration**
  - All viewpoints will be heard
  - Decisions made by consensus or vote
  - Protocol must be evidence based!
- **Protocol approval** required by Institute  
(based on DSMB recommendations)
- Once collaborative protocol is developed
  - **Budgets** revised because all sites doing same activities
  - Potential problem: perceived “ownership” of site’s funding



# Data and Safety Monitoring Board

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- Appointed by the Institute
- Expertise needed for all aspects of trial
  - Study design & statistics
  - Intervention
  - Measurements
  - Ethicist (possibly)
- Include members w/ prior DSMB experience!
- [More by Dr. Harlan]



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# Quality Control, Monitoring, & Oversight

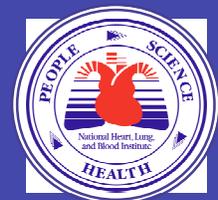
- Recruitment monitoring
- Measurement quality control & monitoring
- Intervention delivery
- Site visits
- Safety & efficacy monitoring  
[next talk - Dr. Harlan]



# Monitoring Recruitment

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- Overall study goals paramount; goals also needed for minorities and women
- Every site needs specific recruitment goals for total and rate (e.g., weekly goal)
- Central monitoring of recruitment – overall and by site; often weekly
- Compare actual to goal rate; look at number in “pipeline”
- Identify problems early; provide help
- Healthful competition useful

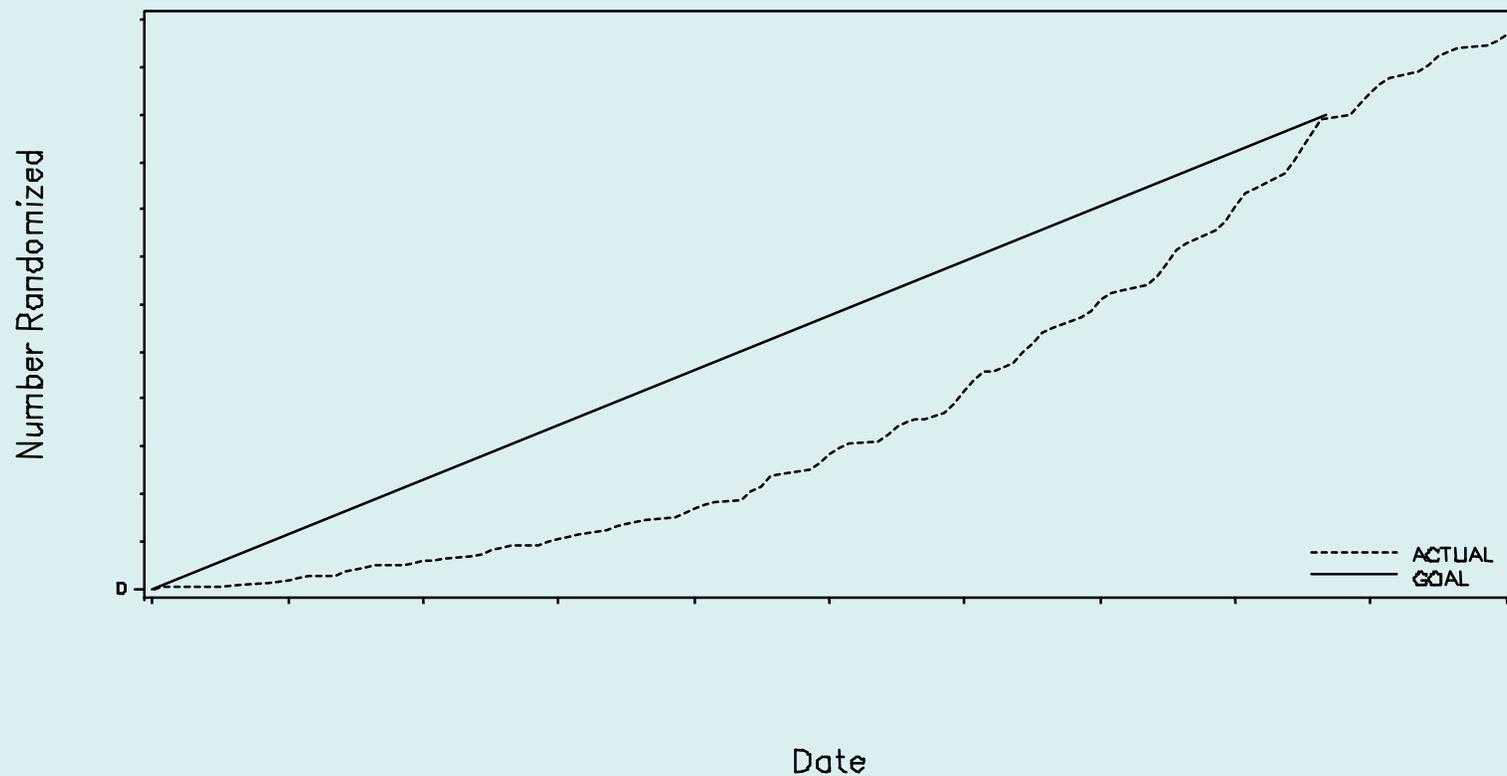


## Example of Recruitment Table

SITE	# Participants Screened			# Participants Randomized			
	Last 7 days	Last 28 days	Total	Last 7 days	Last 28 days	Total	Rank
<b>Overall</b>	<b>25</b>	<b>149</b>	<b>1571</b>	<b>11</b>	<b>217</b>	<b>1027</b>	
<b>Site 1</b>	<b>3</b>	<b>9</b>	<b>245</b>	<b>1</b>	<b>30</b>	<b>177</b>	<b>3</b>
<b>Site 2</b>	<b>8</b>	<b>22</b>	<b>266</b>	<b>2</b>	<b>57</b>	<b>192</b>	<b>6</b>
<b>Site 3</b>	<b>4</b>	<b>62</b>	<b>322</b>	<b>2</b>	<b>28</b>	<b>144</b>	<b>4</b>
<b>Site 4</b>	<b>4</b>	<b>20</b>	<b>243</b>	<b>1</b>	<b>35</b>	<b>161</b>	<b>5</b>
<b>Site 5</b>	<b>3</b>	<b>8</b>	<b>218</b>	<b>3</b>	<b>19</b>	<b>170</b>	<b>1</b>
<b>Site 6</b>	<b>3</b>	<b>28</b>	<b>277</b>	<b>2</b>	<b>48</b>	<b>183</b>	<b>2</b>

# Example of Recruitment Plot

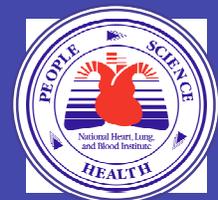
Cumulative Number Randomized



# Quality Control and Monitoring

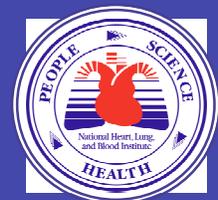
## *Example: PREMIER*

- PREMIER = RCT testing counseling program for **multiple lifestyle behaviors** on BP in persons with higher than optimal BP
- Extensive **monitoring** of measurements, intervention delivery, and retention
- Multi-center investigator-initiated study converted to a **cooperative agreement**



# PREMIER Objective

- To determine the effects on BP of two multi-component behavioral interventions:
  - **ESTABLISHED (EST)** = weight loss, physical activity, reduced dietary sodium
  - **ESTABLISHED PLUS DASH (EST + DASH)** = above plus DASH dietary patterncompared to an Advice Only control group
- To determine the additional effects of the DASH diet beyond ‘established’ recommendations



# PREMIER Design

*Randomization (n=810)*

End of  
Intervention  
(18 months)



Primary  
Outcome  
(6 months)



# PREMIER Interventions

- 18 **counseling** sessions (group and individual) over 6 months using behavioral principles; additional counseling sessions to 18 months
- **Common goals** of both EST and EST + DASH
  - Weight loss  $\geq 15$  lb (6.8 kg) if overweight
  - Physical activity  $\geq 180$  min/wk
  - Sodium intake  $\leq 100$  mmol/d (2,300 mg/d)
- **Additional goals** for EST + DASH group
  - Fruits/vegetables 9-12 servings/day
  - Low-fat dairy products to 2-3 servings/day
  - Saturated fat  $\leq 7\%$  kcal
  - Total fat  $\leq 25\%$  kcal



# PREMIER Outcome Measures

- **Primary outcome:** Change in systolic BP (6 month minus baseline)
- **Secondary outcomes:** Change in diastolic BP, hypertension status at 6 months, BP at 18 months
- **Other measurements**
  - Weight
  - Fitness (heart rate at end of stage 2 of exercise test)
  - 24 Hour urine collections (electrolyte excretion)
  - 24 Hour dietary recalls (fruit/vegetable, dairy, fat)



# Measurement Quality Control and Monitoring: Principles

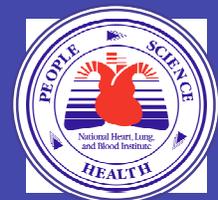
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- Common protocol & procedures for measurements
- Central training for measurements & data entry
  - Didactic and hands on
  - Certification for important measurements
- Monitoring reports reviewed regularly by study committees
- Each measurer identified, corrective training given if needed



# PREMIER Measurement Quality Control and Monitoring

- Measurement & Steering committees reviewed **regular reports** to identify any problems
- BP digit preference report
  - Statistical analysis to determine whether last digit of BP measurement differs from chance
  - Reported by staff (ID number)
  - Significant digit preferences required retraining
- Followup visit analysis
  - Proportion of expected visits & within windows
  - Reported by site
  - To identify problems in follow-up rates early



# Quality Control of Intervention Delivery: Principles

- **Common protocol** and procedures for interventions
- **Central training in intervention**
  - Didactic and hand-on (e.g., role playing)
  - Certification
- **Regular monitoring of intervention delivery (process)**
  - Delivery of specific intervention components
  - Attendance; reasons for missed visits
- **Regular monitoring of intermediate measures (impact)**
  - Physiologic confirmation or self-report of behavior change



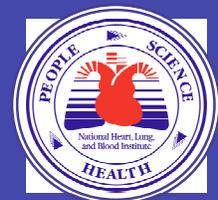
# PREMIER Intervention Monitoring

- Intervention & Steering Committees reviewed **process** data
  - Missed intervention-visit reports
    - By site, randomized group, and visit number
    - Reasons for missed visits; makeup visits
  - Data on diet and physical activity in intervention attendees (collected as part of self-monitoring)
- DSMB monitored impact data:
  - Data on entire denominator in all 3 arms
  - Weight, diet, fitness, urinary sodium, others



# Site Visits: Principles

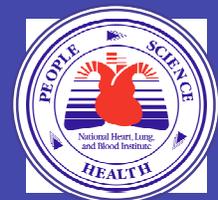
- Routine site visits to monitor:
  - Recruitment strategies
  - Intervention delivery
  - Measurement procedures
  - Data entry procedures
- “For-Cause” site visits when a site appears to be having a problem from the monitoring reports
- Site visit teams
- Written reports with recommendations



# Example: PREMIER Site Visits

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- Regular site visits to the 4 **field centers**
  - Reviewed all study procedures
- Regular site visits of the **CC** by the PO
  - Reviewed all CC functions
- Site visit **teams** included Coordinating Center, Project Office, other field center rep, DSMB member to CC
- **Written** site visit **reports** included recommendations to the site



# PREMIER Intervention Effects

	Baseline	Mean Change from Baseline		
		Advice	EST	EST + DASH
<b>Weight</b>	<b>97 Kg<sup>¶</sup></b>	<b>- 1.1</b>	<b>- 4.9 *</b>	<b>- 5.8 *</b>
<b>Fitness</b>	<b>130 beats/min</b>	<b>- 5.3</b>	<b>- 8.0 *</b>	<b>- 9.0 *</b>
<b>Sodium Intake</b>	<b>173 mmol/24hr</b>	<b>- 21</b>	<b>- 32 *</b>	<b>- 33 *</b>

\* p<0.05 compared to ADVICE, ¶ among overweight participants



# PREMIER Intervention Effects

	Baseline	Mean Change from Baseline		
		ADVICE	EST	EST + DASH
<b>Fruit / Veg</b>	<b>4.6 servings/d</b>	<b>0.5</b>	<b>0.5</b>	<b>3.0 *†</b>
<b>Dairy</b>	<b>1.7 servings/d</b>	<b>0.1</b>	<b>- 0.2 *</b>	<b>0.5 *†</b>
<b>Sat Fat</b>	<b>11% kcal</b>	<b>- 0.4</b>	<b>- 1.5 *</b>	<b>- 3.3 *†</b>
<b>Total Fat</b>	<b>33% kcal</b>	<b>- 1.0</b>	<b>- 3.9 *</b>	<b>- 9.5 *†</b>

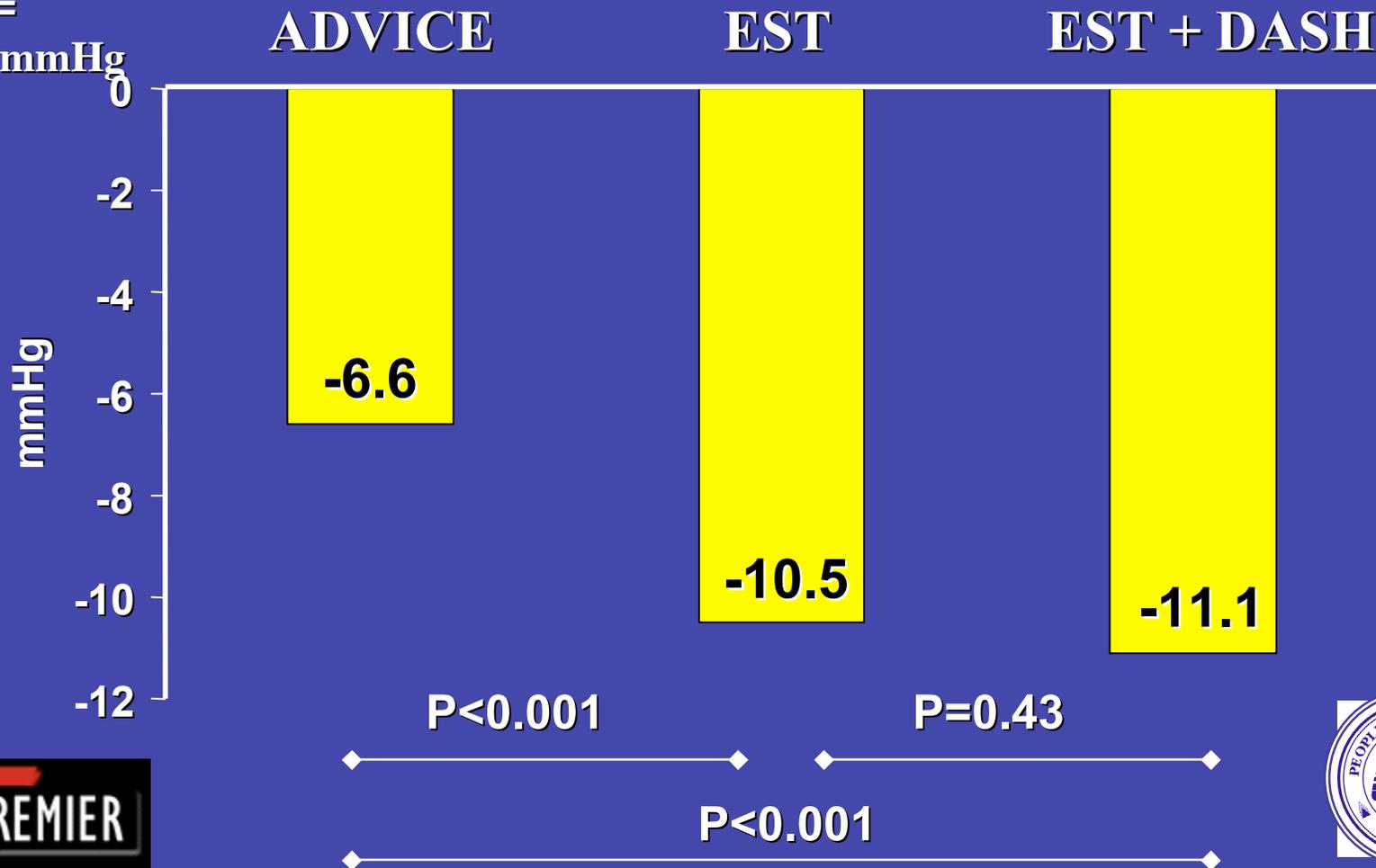


- $p < 0.05$  compared to ADVICE
- †  $P < 0.05$  EST vs EST + DASH



# PREMIER primary results: Mean Reduction in SBP from Baseline

BL =  
135 mmHg



# Summary

- Program staff role varies by type of funding mechanism, investigator- or Institute-initiated, single- or multi-center
- Organizational structure of multicenter studies important for proper implementation
- Quality control and monitoring of studies important for quality research; multi-center studies require substantial staff involvement

