RECRUITMENT AND ADHERENCE STRATEGIES/EXPERIENCE FROM CLINICAL TRIALS

Jeffrey L. Probstfield, MD
University of Washington Schools of Medicine and Public Health
Fred Hutchinson Cancer Research Center
Today's session is being videotaped and recorded for educational purposes. It will be available on the ITHS website for public viewing.
# COMPARISON OF SHEP, STOP-H, MRC-92 AND SYST-EUR CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>SHEP</th>
<th>STOP-H</th>
<th>MRC-92</th>
<th>Syst-Eur</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Size</strong></td>
<td>4736</td>
<td>1627</td>
<td>4396</td>
<td>4695</td>
</tr>
<tr>
<td><strong>Age Range</strong></td>
<td>60+</td>
<td>70-84</td>
<td>65-74</td>
<td>60+</td>
</tr>
<tr>
<td><strong>Mean (n&gt;80)</strong></td>
<td>71.5(650)</td>
<td>75.6(269)</td>
<td>70.3(0)</td>
<td>70.3(?)</td>
</tr>
<tr>
<td><strong>BP Criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>160-219</td>
<td>180-230</td>
<td>160-209</td>
<td>160-219</td>
</tr>
<tr>
<td>DBP</td>
<td>&lt;90</td>
<td>90+</td>
<td>&lt;114</td>
<td>&lt;95</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>Mortality</td>
<td>Stroke</td>
<td>Stroke</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>P R DB</td>
<td>P R DB</td>
<td>P R SB</td>
<td>P R DB</td>
</tr>
</tbody>
</table>
Number of patients randomly assigned treatment


Figure 1
# COMPARISON OF SHEP, STOP-H, MRC-92 AND SYST-EUR CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>SHEP</th>
<th>STOP-H</th>
<th>MRC-92</th>
<th>Syst-Eur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean F/U Time</td>
<td>54 mo</td>
<td>25 mo</td>
<td>70 mo</td>
<td>30 mo</td>
</tr>
<tr>
<td>Baseline BP Mean</td>
<td>170/77</td>
<td>190/104</td>
<td>185/91</td>
<td>174/86</td>
</tr>
<tr>
<td>BP Differential</td>
<td>12/4</td>
<td>19.5/8</td>
<td>14/6</td>
<td>11/5</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to F/U</td>
<td>6</td>
<td>0</td>
<td>25%</td>
<td>P116/A121</td>
</tr>
<tr>
<td>% Crossovers</td>
<td>33</td>
<td>23</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>% Adherence</td>
<td>90/67</td>
<td>84/77</td>
<td>52D/37B/47P</td>
<td>85/72</td>
</tr>
</tbody>
</table>
## COMPARISON OF SHEP, STOP-H, MRC-92 AND SYST-EUR OUTCOMES: PERCENT REDUCTION

<table>
<thead>
<tr>
<th></th>
<th>SHEP</th>
<th>STOP-H</th>
<th>MRC-92</th>
<th>Syst-Eur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Stroke</td>
<td>36</td>
<td>47</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>CHD</td>
<td>27</td>
<td>28</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>LVF</td>
<td>54</td>
<td>48</td>
<td>N/A</td>
<td>36</td>
</tr>
<tr>
<td>CVD</td>
<td>32</td>
<td>40</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>12</td>
<td>43</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>
## SYST - EUR

### A WORST CASE ANALYSIS?

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>STROKE</th>
<th>CHD</th>
<th>TOTAL</th>
<th>LOST TO FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYST-EUR</td>
<td>4695</td>
<td>124 (250)</td>
<td>131</td>
<td>255</td>
<td>237</td>
</tr>
<tr>
<td>Placebo</td>
<td>2297</td>
<td>77</td>
<td>73</td>
<td>150</td>
<td>116</td>
</tr>
<tr>
<td>Active Drug</td>
<td>2398</td>
<td>47</td>
<td>58</td>
<td>105</td>
<td>121</td>
</tr>
<tr>
<td>SHEP</td>
<td>4736</td>
<td>262 (270)</td>
<td>245</td>
<td>507</td>
<td>10</td>
</tr>
<tr>
<td>Placebo</td>
<td>2371</td>
<td>159</td>
<td>141</td>
<td>300</td>
<td>5</td>
</tr>
<tr>
<td>Active Drug</td>
<td>2365</td>
<td>103</td>
<td>104</td>
<td>207</td>
<td>5</td>
</tr>
</tbody>
</table>
RECRUITMENT

• Successful recruitment has been documented in many trials: Government and Industry.
• Clinical Sites: Past performance predicts future
• Your centers carefully selected: past performance

(http://www.fhcrc.org/science/phs/swog/recrcct/)
RECRUITMENT: FUNDAMENTAL POINT

Friedman, Furberg and DeMets:

Successful recruitment depends on developing a careful plan with multiple strategies, maintaining flexibility, establishing interim goals and preparing to devote the necessary effort.
RECRUITMENT OF STUDY POPULATION

“GET SUFFICIENT POPULATION, IN REASONABLE TIME”

RECRUITMENT FAILURE OCCURS

• LATE START
• INADEQUATE PLANNING
• INSUFFICIENT EFFORT
• OVERLY OPTIMISTIC EXPECTATIONS
RECRUITMENT: BASIC ISSUES

• Planning-sources and support
• Strategies and sources
• Conduct-implementation
• Monitoring-short and long term goals
• Problems-expect them to happen
• Solutions-make them occur
• Reasons for Participation
ADVANTAGES: WIDE ENTRY CRITERIA

• Easier screening and recruitment
• More feasible and affordable
• Broader range of variables and larger study size
• More reliable overall result
• Greater public health Impact
• Better opportunity to test subgroup hypotheses
PLANNING

- Likelihood of getting sufficient participants
- Statistical power-assumes constant enrollment
- Staff-organized and experience
- Institutional support-proper facilities
- Publicity- start before trial
- Multiple strategies- at least 3
- Pilot test strategies
- Contingency plans
## RECRUITMENT DATA: 13 NHLBI STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Participants</th>
<th>Recruitment Time</th>
<th>Person-Years in Planned Recruitment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual/Planned</td>
<td>Actual/Planned</td>
<td>Actual/Planned (R)</td>
</tr>
<tr>
<td>AMIS</td>
<td>4,524 1.06</td>
<td>1.00</td>
<td>0.83</td>
</tr>
<tr>
<td>BHAT</td>
<td>3,837 0.95</td>
<td>1.21</td>
<td>0.82</td>
</tr>
<tr>
<td>CAPS</td>
<td>502 1.00</td>
<td>1.08</td>
<td>0.82</td>
</tr>
<tr>
<td>CARDIA</td>
<td>5,182 1.02</td>
<td>1.00</td>
<td>0.86</td>
</tr>
<tr>
<td>CDP</td>
<td>8,345 1.00</td>
<td>1.22</td>
<td>0.55</td>
</tr>
<tr>
<td>CSSCD</td>
<td>3,241 1.01</td>
<td>1.13†</td>
<td>1.16</td>
</tr>
<tr>
<td>HDFP</td>
<td>10,940 1.04</td>
<td>1.50</td>
<td>1.02</td>
</tr>
<tr>
<td>LRC</td>
<td>3,843 1.08</td>
<td>1.54</td>
<td>0.34</td>
</tr>
<tr>
<td>MILIS</td>
<td>985 0.82</td>
<td>2.71</td>
<td>0.35</td>
</tr>
<tr>
<td>MRFIT</td>
<td>12,886 1.07</td>
<td>1.13†</td>
<td>0.81</td>
</tr>
<tr>
<td>POSCH</td>
<td>838 0.84</td>
<td>1.58†</td>
<td>0.25</td>
</tr>
<tr>
<td>SHEP Pilot</td>
<td>551 1.10</td>
<td>1.17</td>
<td>0.71</td>
</tr>
<tr>
<td>TIMI-1*</td>
<td>316 0.93</td>
<td>0.96</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*TIM-1 was stopped on the recommendation of Data and Safety Monitoring Committee; the treatment showed strong evidence of efficacy.

† The 'projected' time was revised after additional clinics joined the study.
RECRUITMENT EFFICIENCY

CONT CLIN TRIALS 1987;8:141S-149S
RECRUITMENT EFFICIENCY

CONT CLIN TRIALS 1987;8:141S-149S
RECRUITMENT EFFICACY

![Graph showing recruitment efficiency over time. The graph compares projected and actual cumulative percentages.](image-url)
PATIENTS RANDOMIZED

CHARM - Randomisation updated: 2001-03-16
All three studies, Total

Week

Patients randomised
Actual accrual as of March 31, 2004: 24,166

Reach accrual goal of 32,400 at end of April 2004
ACCORD VANGUARD
ACCORD
MAIN TRIAL

- Number Randomized:
  - 0
  - 1000
  - 2000
  - 3000
  - 4000
  - 5000
  - 6000
  - 7000
  - 8000
  - 9000
  - 10000

- Weeks:
  - 0
  - 10
  - 20
  - 30
  - 40
  - 50
  - 60
  - 70
  - 80
  - 90
  - 100
  - 110
  - 120
  - 130
  - 140
  - 150

- Number of Sites Active:
  - 0
  - 20
  - 30
  - 40
  - 50
  - 60
  - 70
  - 80

- Graph:
  - X-axis: Weeks
  - Y-axis: Number Randomized
  - Dashed line: ACTUAL
  - Solid line: GOAL
STRATEGIES AND SOURCES

POINTS OF EMPHASIS

• Strategies are unpredictable
• Good relationship with medical community
• Respect families and significant others
• Do not be overly aggressive
  – run-in period
• Combinations of approaches
RECRUITMENT STRATEGIES IN CONTROLLED TRIALS

Chart Review

Media Efforts
Direct Mail
Mass Screening
Laboratory Lists

Registries
Blood Bank Donors
Occupational Screening
Medical Referrals
NEW STRATEGY

- WEB-SITE SCREENING TOOL
- LIMITED INFORMED CONSENT
- ENDORSED BY IG OF USA
- QUALIFIED SCREEENEES TO GEOGRAPHICALLY CLOSEST CLINIC
- CCC AGREED TO WORK OUT PROGRAMMING
- RETAIN DATA WITHOUT IDENTIFIERS AT CCC
LESSONS LEARNED FROM MASS MAILING

• Integrate into overall recruitment program
• “Targeted” population-e.g. age, ethnicity
• Post card prompt
  – Return
  – Phone
• Telephone follow-up
• Repeat mailing same list
RECRUITMENT OF MINORITIES

• SELECT SITES WITH MINORITIES
  – MUST BE INVITED
  – MAY NEED HELP WITH APPLICATION
  – ADDITIONAL TRAINING MAY BE REQUIRED

• NON-MINORITY SITES: MINORITY STAFF
  – INVOLVEMENT: LOCAL MINORITY PHYSICIANS

• COMMUNITY APPROACHES DIFFERENT
  – CHURCHES, FAMILY EVENTS

• INCENTIVES MAY BE DIFFERENT
CONDUCT

- Successful implementation
- Logging activities: recruitment source
- Respect participant privacy
- Prescreening helps workload
- Smooth clinic operation essential
- Regular staff meetings
- Record keeping crucial
CROSS-TRAINING STAFF

• STAFF: ALWAYS ABLE TO DO ALL THINGS
• STAFFING LIMITATIONS-NOT ALL CAN
  – DURING RECRUITMENT-IT MUST CONTINUE
• WE HAVEN’T DONE IT WELL ENOUGH
• WE MUST DO BETTER
  – STAFF ABSENCES FOR ANY REASON
MONITORING

• Establish long and short term goals
  – overall and by clinical center
• Tables, graphs and charts
  – overall and by clinical center
• Identify reasons if lagging
  – overall and by clinical center
• Establish role models-use as a resource
RECRUITMENT: CAREFUL PLANNING

• BE CONSERVATIVE IN YOUR ESTIMATES
• Establish interim goals
• Have contingency plans

• 3 TO 6 MONTH PERIOD TO SEE RESULTS
Expect them—they will occur

- Inadequate funding for screening process
- Unwillingness to refer or allow participation
- Overestimation of prevalence
- Overly rigorous entry criteria
SOLUTIONS

• Accept a smaller sample size
• Relax inclusion/exclusion criteria
• Extend enrollment time
• Change the design
• Recycle previous ineligibles
SOLUTIONS

- ACCEPT A SMALLER SAMPLE SIZE - X
- RELAX INCLUSION/EXCLUSION CRITERIA - X
- EXTEND THE TIME FOR ENROLLMENT - X?
- CHANGE THE DESIGN - X
- RECYCLE PREVIOUS INELIGIBLES - O
AVOIDING SLUMPS: PRACTICAL APPROACHES

• WE MUST AVOID FUTURE SLUMPS
• CROSS TRAINING
• STAFF-VACATIONS NOT AT SAME TIME
• HOLIDAYS-THANKSGIVING, CHRISTMAS/NEWYEARS
  – PRELOAD
  – POSTLOAD
REASONS FOR PARTICIPATION

• Answer scientific question accurately
• Benefit other patients-current and future
• Benefit to themselves-quality of care
  – additional monitoring
  – second opinion of their condition
  – reassurance regarding diagnosis
OVERALL RECRUITMENT PROGRAM (1)

• Start recruitment on target date
• Choose physically accessible location
• Use at least three recruitment strategies
• Recruitment Coordinator—overall responsibility
• Trial-wide recruitment coordinator network
• Accurate tracking system
• Match staff and screenees
OVERALL RECRUITMENT PROGRAM (2)

- Provide staff back-up
- Be aware and anticipate staff burnout
- Inform medical and lay communities
- Recruits-solicit in simple language
- Medical associations and hospital staffs-contacted by the Principal Investigator
OVERALL RECRUITMENT PROGRAM (3)

• Identify excellent staff
• Calendar for ENTIRE recruitment period
• Pretest your recruitment strategies
• Regular review and evaluation of program
• Develop contingency plans
• Flexible clinic hours
CLINICAL TRIALS OVERVIEW

FUNDAMENTAL POINT: PARTICIPANT ADHERENCE

Many potential adherence problems can be prevented or minimized before participant enrollment. Once a participant is enrolled, taking measures to enhance and monitor participant adherence is essential.
SAMPLE SIZE ADJUSTMENT FOR REDUCED ADHERENCE

Key Point - Adherence correction term-sample size formula, a squared function.

\[ 2N = \sigma^2(z_\alpha + z_\beta)^2 \div (\mu_1 - \mu_2)^2(1-p)^2 \]

\( p \) = Reduction in Adherence
\( k \) = Increase in Sample Size

<table>
<thead>
<tr>
<th>( p )</th>
<th>( k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>.01</td>
<td>1.02</td>
</tr>
<tr>
<td>.05</td>
<td>1.11</td>
</tr>
<tr>
<td>.10</td>
<td>1.23</td>
</tr>
<tr>
<td>.20</td>
<td>1.56</td>
</tr>
<tr>
<td>.30</td>
<td>2.04</td>
</tr>
<tr>
<td>.50</td>
<td>4.00</td>
</tr>
</tbody>
</table>
OVERALL ADHERENCE PLAN (1)

• Develop a bottom line - cannot be transgressed (Minimum amount of data which is essential)

• Set goals depending on protocol
  – “Acceptability” trial
  – “Alteration of natural history” trial

• Recruitment
  – Don’t randomize all “number eligibles”
  – Do use run-in and test dosing procedures
OVERALL ADHERENCE PLAN (2)

- Pay attention to signs and symptoms of potential poor adherence
- Adherence team approach
- Constant care taker model
- Optimization of dosing regimen
- Teach adherence techniques
- Use behavioral counseling approach (Interviewing and counseling skills)
- Have an intervention plan for poor adherers
- Have a maintenance plan for everyone
BOTTOM LINE: MINIMUM ACCEPTABLE ADHERENCE

Know primary outcome status on every randomized participant.

Human behavior will allow few to purposely harm a worthy scientific project.
"RUN-IN" PERIOD

- Pre-randomization procedure
- Single blind
- Placebo used
- Test for "pill-taking behavior"
“TEST-DOSING” PERIOD

- Pre-randomization procedure
- Single blind
- Active drug used
- Identify those with severe adverse effects
# ADHERENCE PERFORMANCE

## TEST-DOSING AND RUN-IN

*(NUMBERS EXCLUDED)*

<table>
<thead>
<tr>
<th></th>
<th>Test-Dosing</th>
<th>Run-In</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>7,450</td>
<td>7,065</td>
</tr>
<tr>
<td>Intolerance</td>
<td>149</td>
<td>6</td>
</tr>
<tr>
<td>Poor Adherence</td>
<td>164</td>
<td>140</td>
</tr>
<tr>
<td>Total Excluded</td>
<td>385</td>
<td>265*</td>
</tr>
</tbody>
</table>

*478 screenes had two run-in periods*
Repeat Placebo Run-in Effectiveness
Proportion achieving 80% adherence, by group

<table>
<thead>
<tr>
<th>GROUP</th>
<th>one run-in</th>
<th>two run-in</th>
</tr>
</thead>
</table>

- **MEAN**
  - 1.0
  - 0.9
  - 0.8
  - 0.7
  - 0.6
  - 0.5
  - 0.4
  - 0.3
  - 0.2
  - 0.1
  - 0.0

- **VISIT NUMBER**
  - 2 WEEKS
  - 5 WEEKS
  - 1 YEAR
  - 3 YEARS
  - 4 YEARS
CONCLUSIONS ABOUT
“PLACEBO RUN-IN PERIOD”

What does it do

• Identifies a group of individuals who don’t adhere well during designated run-in
• Successful repeat run-in performers (6.9%) adhere less well during trial
• Those identified representative of those enrolled

What doesn’t it do

• Identify all who will adhere poorly to intervention

Uncertainties

• If those who “fail” would all be poor adherers
• Cost/Benefit-advantageous
GENERALIZIBILITY
“INTENTION TO TREAT,” “ONCE IN, ALWAYS COUNTED” (1)

• Issue: Avoid bias

• Fundamental Point: Excluding randomize subjects from analysis and sub-grouping on the basis of the outcome or response variables and lead to biased results. This bias can be of unknown magnitude and direction.
“INTENTION TO TREAT,”
“ONCE IN, ALWAYS COUNTED” (2)

“Preserves the benefits of randomization by including all randomized patients based on their original allocation.”

Safeguards against:

Erroneous claims of efficacy by exclusion of those who do not adhere to the protocol
WHAT IS A PI?

“Principal Investigator,”
or “Practically Invisible”

Clinical sites most successful where the PI is engaged and actively involved.

Coordinators-- be proactive and identify activities where PI can help you!
PRINCIPAL INVESTIGATOR DUTIES

• Select appropriate staff
• Give Coordinators authority
• Develop recruitment plan (with RC)
• Selection of R and A strategies (with C)
• Utilize appropriate monitoring system
• Be flexible and receptive to change in plans
• Inform medical and lay community
RECRUITMENT OF STUDY POPULATION

“GET SUFFICIENT POPULATION, IN REASONABLE TIME”

RECRUITMENT FAILURE OCCURS

• LATE START
• INADEQUATE PLANNING
• INSUFFICIENT EFFORT
• OVERLY OPTIMISTIC EXPECTATIONS
WHAT WE NEED TO BE SUCCESSFUL

- EVERY CLINIC RANDOMIZING ON A REGULAR BASIS
- LOCAL PI INVOLVEMENT
- REGULAR MEETINGS OF CLINIC STAFFS
- REGULAR REVIEW OF RECRUITMENT DATA LOCALLY
- ELIMINATE STRATEGIES THAT ARE NOT WORKING
- IMPLEMENT OTHER’S SUCCESSFUL STRATEGIES
ITHS Clinical Research Education Series – Future Talks

• **Tuesday, Feb. 3rd at 12pm** - *Principles of Study Design and Statistical Analysis* presented by Mary J. Emond, PhD, Assoc. Professor, Biostatistics

• **Tuesday, Mar. 3rd at 12pm** - *Putting the “Informed” in the Informed Consent Process* presented by Zuraya Aziz & Halle Showalter Salas, MPhil, Research Subject Advocates, Seattle Children’s