Translating pilot studies into larger clinical trials

Twelve Commandments

Marco Pahor, MD
University of Florida Institute on Aging

www.aging.ufl.edu
Thor Shalt

1. Have a vision, think backwards, and set a timeline
2. Start early. Complete early. Time is your best friend
3. Work hard. Invest >1000% effort
4. Shoot high, be persistent, and be patient
5. Capitalize on teams and leverage existing strengths
6. Engage the best experts around the country
7. Tell a strong story in a way that anyone can understand
8. Follow a logical flow and use conceptual models
9. Be innovative and market your project
10. Conduct pilot studies
11. Know and outline upfront the aim of the main study
12. Conduct secondary analyses of existing cohort studies
Lifestyle Interventions and Independence for Elders

The LIFE Study

Is a structured **physical activity** or a **health education** program more effective in reducing the risk of major mobility disability in older persons?
- Multicenter, single-blinded, parallel randomized trial
- 8 field centers across the US
- Coordinating Center: University of Florida
- Data Management Quality Control: Wake Forest University
- Duration: February 2010 – December 2013
LIFE Pilot Study
State upfront the goal of the main LIFE trial

While several studies consistently suggest a benefit of physical exercise on disability and function, definitive evidence is lacking that exercise prevents the onset of disability (including mobility disability) in older persons. A Phase 3 randomized, controlled trial (RCT) is needed, but preliminary data to estimate the sample size for such a trial are currently insufficient. Additional feasibility data also should be gathered before such a trial can be effectively designed and implemented.
LIFE Pilot study aims 1

• To obtain data that will allow a more accurate projection of the **sample size needed for a full-scale** study by using the incidence rates of the outcome of major mobility disability (defined as being unable to walk 400 m) and the drop-in, drop-out and loss to follow-up rates.

• To provide **internal validity of the efficacy** of the exercise intervention by assessing its effects on the SPPB and the 400 m gait speed
LIFE Pilot study aims 2

• To assess protocol feasibility and participant adherence and retention in the intervention group and in the control group, to refine these protocols, and to assess their replicability and quality control across multiple sites.

• To assess the rates of intercurrent illness that may compromise adherence to the intervention, and to assess the feasibility of an exercise protocol to accommodate these events.
LIFE Pilot study aims 3

• To assess the feasibility and yields of recruiting this at-risk population from diverse communities and ethnic subgroups, and to refine the recruitment strategies.

• To assess the psychosocial and health-related early predictors of response and adherence to the exercise intervention so that participants requiring increased efforts.
LIFE Pilot study aims 4

- To optimize the multicenter infrastructure
  - Field centers, administrative coordinating center, data coordination center, ECG reading center, biological samples repository, and committees
  - Developing and refining study forms
  - Developing a web-based communications system
  - Programming a data management system
  - Preparing study MOPS and recruitment materials
  - Establishing a study-wide system for quality control
  - Developing a comprehensive system to monitor and ensure participant safety
Means estimated from repeated measures ANCOVA adjusted for gender, field center and baseline values.

Pahor et al. *J Gerontol* 2006;61:1157
Means estimated from repeated measures ANCOVA adjusted for gender, field center and baseline values.

LIFE-Pilot - Cumulative hazard mobility disability

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>SA</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>211</td>
<td>213</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative endpoints

<table>
<thead>
<tr>
<th></th>
<th>SA</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Years since randomization

<table>
<thead>
<tr>
<th>Years</th>
<th>Cumulative Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>1.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

- Successful aging
  - Physical activity
  - p=0.25
  - HR=0.74, 95%CI=[0.44,1.24]

HABC – 400 m walk performance and mobility disability

Newman et al. JAMA; 2006;295:2018
Distribution of Performance in Those With & Without Mobility Disability

Reliability of the 400-M Usual-Pace Walk Test as an Assessment of Mobility Limitation in Older Adults

Yves M. Rolland, MD, Matteo Cesari, MD, Michael E. Miller, PhD, Brenda W. Penninx, PhD, Hal H. Atkinson, MD, and Marco Pahor, MD

Table 2. Characteristics of the Test (Test 1) and Retest (Test 2) for the 400-M Walk Test (N = 60)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Test 1</th>
<th>Test 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unable to perform 400-m walk test, n (%)</td>
<td>19 (31.7)</td>
<td>19 (31.7)</td>
<td>1.00*</td>
</tr>
<tr>
<td>Number of rest stops per subject, mean ± SD †</td>
<td>0.7 ± 1.5</td>
<td>0.4 ± 0.8</td>
<td>.21</td>
</tr>
<tr>
<td>ΔHR, mean ± SD ‡</td>
<td>11.9 ± 7.7</td>
<td>11.8 ± 7.5</td>
<td>.98</td>
</tr>
<tr>
<td>Distance of walk, m, mean ± SD</td>
<td>315.2 ± 137.6</td>
<td>312.4 ± 139.0</td>
<td>.87</td>
</tr>
<tr>
<td>Time of rest stops, seconds, mean ± SD †</td>
<td>10.1 ± 24.5</td>
<td>6.4 ± 16.4</td>
<td>.32</td>
</tr>
<tr>
<td>Reasons stopped testing, n (%) †</td>
<td></td>
<td></td>
<td>.92</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (89.5)</td>
<td>15 (78.9)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (15.8)</td>
<td>1 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1 (5.3)</td>
<td>1 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (21.1)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td>400-m test speed, m/s, mean ± SD</td>
<td>0.84 ± 0.18</td>
<td>0.86 ± 0.19</td>
<td>.63</td>
</tr>
<tr>
<td>4-m walk speed, m/s, mean ± SD ‡</td>
<td>0.77 ± 0.24</td>
<td>0.80 ± 0.24</td>
<td>.40</td>
</tr>
</tbody>
</table>

* Kappa test.
Reliability of the 400-M Usual-Pace Walk Test as an Assessment of Mobility Limitation in Older Adults

Yves M. Rolland, MD,* † Matteo Cesari, MD, * Michael E. Miller, PhD, * Brenda W. Penninx, PhD,* Hal H. Atkinson, MD,* and Marco Pahor, MD*

Figure 1. Predicted probability of disability to perform the 400-m walk test based on walking speed in the 4-m walk test (logistic regression).

JAGS 52:972–976, 2004
Events

Physical Activity: 30.1% (n=246/818)
Health Education: 35.5% (n=290/817)

HR=0.82, 95%CI=0.69-0.98
P=0.03

Pahor et al JAMA 2014;311:2387
Events

Physical Activity: 14.7% (120/818)
Health Education: 19.8% (162/817)

HR=0.72, 95%CI=0.57-0.91
p=0.006

Pahor et al JAMA 2014;311:2387
Do you qualify for The Testosterone Trial?

✓ Do you have trouble walking a quarter of a mile?
✓ Are you concerned about low energy?
✓ Do you have less interest in sex?

If you answered YES to at least one of these three questions, you may qualify for The Testosterone Trial.

Why The T Trial is important

The goal of The National Institute on Aging, a sponsor of this trial, is to improve the health and well-being of older Americans through research. Some experts estimate that 4 to 5 million men in the U.S. have low testosterone levels. The Testosterone Trial may help us learn if testosterone treatment improves the health and well-being of older men who have low testosterone. By participating in this study, you may help men of your generation and beyond—even your own sons and grandsons.
Do you qualify for The Testosterone Trial?

✓ Do you have trouble walking a quarter of a mile?
✓ Are you concerned about low energy?
✓ Do you have less interest in sex?

If you answered YES to at least one of these three questions, you may qualify for The Testosterone Trial.

Why The T Trial is important

The goal of The National Institute on Aging, a sponsor of this trial, is to improve the health and well-being of older Americans through research. Some experts estimate that 4 to 5 million men in the U.S. have low testosterone levels. The Testosterone Trial may help us learn if testosterone treatment improves independent living and quality of life. By participating in this study, you may help men of your generation and beyond—even your own sons and grandsons.

Research supported by The National Institutes of Health

All photographs are of models and the images are being used for illustrative purposes only.

With age comes wisdom

... and a whole lot more.

If you have trouble:
- Climbing stairs
- Walking a quarter of a mile
- Having enough energy to do normal tasks

Consider joining The Testosterone Trial
A national study for older men

718-405-8271
Einstein in the Media

The New York Times interviews Nir Barzilai, M.D., on the development of self-driving cars to serve older adults. Dr. Barzilai is the Ingeborg and Ira Leon Rennert Chair of Aging Research and director of the Institute for Aging Research at Einstein.

(Thursday, March 23, 2017)

The Washington Post interviews Nir Barzilai, M.D., about Donald Trump's health, human aging, and questions about the factors affecting longevity and healthspan. Dr. Barzilai is the Ingeborg and Ira Leon Rennert Chair of Aging Research and director of the Institute for Aging Research at Einstein.

(Wednesday, January 18, 2017)

U.S. News & World Report interviews Ana Maria Cuervo, M.D., Ph.D., and Nir Barzilai, M.D., about their aging research. Drs. Cuervo and Barzilai are co-directors of Einstein's Institute for Aging Research.

(Tuesday, August 09, 2016)

The New York Times interviews Dr. Nir Barzilai, M.D., about his upcoming clinical trial to determine if an existing FDA-approved drug can extend health span. Dr. Barzilai and his collaborators at the American Federation for Aging Research will investigate if metformin, a cheap and commonly used medication to treat type 2 diabetes, can delay the onset of several age-related diseases. Dr. Barzilai is the Ingeborg and Ira Leon Rennert Chair of Aging Research and director of the Institute for Aging Research at Einstein.

(Monday, February 01, 2016)

More coverage on this story

The Washington Post

National Geographic highlights the leadership role Nir Barzilai, M.D., is taking in a clinical trial to determine if a common diabetes drug can delay aging. Dr. Barzilai notes that the goal of the Targeting Aging with Metformin (TAME) study is not to find the "fountain of youth," but to extend the number of healthy, active years humans can enjoy. Dr. Barzilai is the Ingeborg and Ira Leon Rennert Chair of Aging Research and director of the Institute for Aging Research at Einstein.

(Thursday, December 03, 2015)

More coverage on this story

Forbes
Fox News
PIX 11
National Post (Canada)
The Telegraph
Newsweek
Innovation

To effectively address the emerging clinical research needs of the older populations and to promote all stages of translational research we propose to construct the **IOA-CTRB of 39,500 GSF**, a Leadership in Energy and Environmental Design (LEED) platinum building. The IOA-CTRB will host the following new shared resources, which are designed to enhance the UF research capacity, and to provide novel behavioral intervention facilities not currently available on campus..................
Pepper center theoretical conceptual model

Figure B.1.2.1. Mobility in the context of the International Classification of Function (ICF)

- **Biology**:
  - Inflammation, neural transmission, hormones, proteolysis, autophagy, apoptosis, satellite cells, oxidative stress, energy production, blood flow

- **Body function & structure**:
  - Sarcopenia

- **Disease**:
  - Metabolic, pulmonary, vascular, immune, organ-specific

- **Aging**

- **Environmental Factors**

- **Personal factors**

- **↓ Mobility**
  - Activity limitations: Difficulties in executing tasks
  - Participation: In life situations

- **↓ Physical Performance**
  - Dynapenia

- **↑ Healthcare cost**
  - Caretaker stress
  - Independence
Figure B.1.2.2. Interventions and mechanisms related to mobility and disability prevention.
EPESE - IL-6 and 4 year incident mobility disability

- Adjusted probability
- 95% CI

Ln (IL-6) vs. Probability

n=633

2.5 pg/ml

Ferrucci et al. JAGS 1999;47:639
HABC - Inflammation markers by mobility disability

CRP (mg/L) and IL-6 (pg/mL) levels in participants with and without incident disability. Both CRP and IL-6 levels are significantly higher in participants with incident disability compared to those without, with p-values < .001. Data from Penninx et al. JAGS 2004;52:1105.
<table>
<thead>
<tr>
<th>tertile</th>
<th>incidence</th>
<th>RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>22.2%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>26.9%</td>
<td>1.05</td>
<td>0.88-1.26</td>
</tr>
<tr>
<td>III</td>
<td>41.4%</td>
<td>1.40</td>
<td>1.18-1.68</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>19.8%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>30.6%</td>
<td>1.34</td>
<td>1.11-1.62</td>
</tr>
<tr>
<td>III</td>
<td>40.2%</td>
<td>1.65</td>
<td>1.37-1.98</td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25.0%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28.7%</td>
<td>1.09</td>
<td>0.91-1.30</td>
</tr>
<tr>
<td>III</td>
<td>36.1%</td>
<td>1.18</td>
<td>0.99-1.41</td>
</tr>
</tbody>
</table>

*adjusted for age, gender, race, education, fat mass, smoking, CVD, COPD, diabetes, cancer, arthritis, NSAIDs, corticosteroids albumin, creatinine, EPESE perf.

Penninx et al JAGS 2004;52:1105
ENabling Reduction of low-Grade Inflammation in Seniors - Pilot Study

Funding: NIA U01AG050499
Abbott grant for study drug – the company has no other involvement with the study

Manini et al JAGS in press 2017
- Double-blinded, 2x2 factorial randomized pilot trial
- 5 field centers
- Coordinating Center: University of Florida
- Data Management Quality Control: Wake Forest University
- n=300 – follow-up duration 12 months
Specific Aims

Conduct a pilot RCT in 300 older persons at risk of mobility decline to assess:

– Compared with placebo, the effects of losartan, \( \omega \)-3, and losartan+\( \omega \)-3 on IL-6 and walking speed;
– The recruitment yields, the target population, adherence, retention, tolerability of the interventions
– The primary outcome, sample-size, design, and cost for the main trial;
– The intra-subject variability of IL-6,
– The dosage and safety of the interventions

Manini et al JAGS in press 2017
The ENRGISE Pilot Study will provide preliminary data to design a definitive clinical trial to assess whether the reduction of chronic low-grade inflammation may prevent major mobility disability.
MoTrPAC is a national research consortium designed to discover and perform preliminary characterization of the range of molecular transducers (the “molecular map”) that underlie the effects of physical activity in humans during a six year period. The program’s goal is to study the molecular changes that occur during and after exercise and ultimately to advance the understanding of how physical activity improves and preserves health. The program is the largest targeted NIH investment of funds into the mechanisms of how physical activity improves health and prevents disease.

The MoTrPAC program is supported by the NIH Common Fund and is managed by a trans-agency working group representing multiple NIH institutes and centers, led by the NIH Office of Strategic Coordination, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Aging, and National Institute of Biomedical Imaging and Bioengineering.
MoTrPAC
Molecular Transducers of Physical Activity Consortium

### Bioinformatics Center

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and City</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashley, Euan A.</td>
<td>Stanford University</td>
<td>CA</td>
</tr>
</tbody>
</table>

### Chemical Analysis Sites

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and City</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adkins, Joshua N.</td>
<td>Pacific Northwest National Lab, Richland, WA</td>
<td></td>
</tr>
<tr>
<td>Burant, Charles F. (contact)</td>
<td>University of Michigan, Ann Arbor, MI</td>
<td></td>
</tr>
<tr>
<td>Li, Jun</td>
<td>University of Michigan</td>
<td>MI</td>
</tr>
<tr>
<td>Geszten, Robert E. (contact)</td>
<td>Broad Institute, Inc./Beth Israel Deaconess Medical Center, Boston, MA</td>
<td></td>
</tr>
<tr>
<td>Carr, Steven A.</td>
<td>Broad Institute, Inc./Beth Israel Deaconess Medical Center, Boston, MA</td>
<td>MA</td>
</tr>
<tr>
<td>Clisch, Clary B.</td>
<td>Broad Institute, Inc./Beth Israel Deaconess Medical Center, Boston, MA</td>
<td>MA</td>
</tr>
<tr>
<td>Newgard, Christopher B.</td>
<td>Duke University, Durham, NC</td>
<td></td>
</tr>
<tr>
<td>Jones, Dean Paul</td>
<td>Emory University, Atlanta, GA</td>
<td></td>
</tr>
<tr>
<td>Naft, K. Sreekumaran (contact)</td>
<td>Mayo Clinic Rochester, Rochester, MN</td>
<td>MN</td>
</tr>
<tr>
<td>Lanza, Jan R.</td>
<td>Mayo Clinic Rochester</td>
<td>MN</td>
</tr>
<tr>
<td>Sealjon, Stuart C. (contact)</td>
<td>Icahn School of Medicine at Mount Sinai, New York, NY</td>
<td>NY</td>
</tr>
<tr>
<td>Walsh, Martin John</td>
<td>Icahn School of Medicine at Mount Sinai, New York, NY</td>
<td>NY</td>
</tr>
<tr>
<td>Snyder, Michael P. (contact)</td>
<td>Stanford University, Stanford, CA</td>
<td>CA</td>
</tr>
<tr>
<td>Montgomerey, Stephen B.</td>
<td>Stanford University, Stanford, CA</td>
<td>CA</td>
</tr>
</tbody>
</table>

### Clinical Centers

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and City</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barmann, Marcos M. (contact)</td>
<td>University of Alabama at Birmingham, Birmingham, AL</td>
<td>AL</td>
</tr>
<tr>
<td>Goodpastor, Britt M.</td>
<td>Florida Hospital, Orlando, FL</td>
<td>FL</td>
</tr>
<tr>
<td>Trappe, Scott</td>
<td>Ball State University</td>
<td>IN</td>
</tr>
<tr>
<td>Jakicic, John M.</td>
<td>University of Pittsburgh</td>
<td>PA</td>
</tr>
<tr>
<td>Kohnert, Wendy M.</td>
<td>University of Colorado Denver</td>
<td>CO</td>
</tr>
<tr>
<td>Kraus, William E.</td>
<td>Duke University, Durham, NC</td>
<td>NC</td>
</tr>
<tr>
<td>Rasmussen, Blake B. (contact)</td>
<td>University of Texas Medical Branch Galveston, Galveston, TX</td>
<td>TX</td>
</tr>
<tr>
<td>Musi, Nicholas</td>
<td>University of Texas Health Science Center, San Antonio, TX</td>
<td>TX</td>
</tr>
<tr>
<td>Ravussin, Eric (contact)</td>
<td>LSU Pennington Biomed Research Center, Baton Rouge, LA</td>
<td>LA</td>
</tr>
<tr>
<td>Rankin, Tuomo</td>
<td>LSU Pennington Biomed Research Center, Baton Rouge, LA</td>
<td>LA</td>
</tr>
<tr>
<td>Cooper, Dan M. (contact)</td>
<td>University of California-Irvine, Irvine, CA</td>
<td>CA</td>
</tr>
<tr>
<td>Raddo-Aziki, Shlomit</td>
<td>University of California-Irvine, Irvine, CA</td>
<td>CA</td>
</tr>
</tbody>
</table>

### Consortium Coordinating Center

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and City</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pankow, Marco C.</td>
<td>University of Florida</td>
<td>FL</td>
</tr>
<tr>
<td>Miller, Michael E.</td>
<td>Wake Forest Baptist Medical Center, Winston-Salem, NC</td>
<td>NC</td>
</tr>
<tr>
<td>Rejeski, Walter John</td>
<td>Wake Forest University</td>
<td>NC</td>
</tr>
<tr>
<td>Tracy, Russell P.</td>
<td>University of Vermont</td>
<td>VT</td>
</tr>
</tbody>
</table>

### Footer

*National Institute of Arthritis and Musculoskeletal and Skin Diseases*
*National Institute of Biomedical Imaging and Bioengineering*
*National Institute of Diabetes and Digestive and Kidney Diseases*
*National Institutes of Health*
*Office of Strategic Coordination - The Common Fund*
*National Institute on Aging*
MoTrPAC Consortium Coordinating Center Team

University of Florida, University of Vermont, Wake Forest Baptist Medical Center, Wake Forest University
Twelve Commandments to achieve large clinical trials

**Thou Shalt**

1. Have a vision, think backwards, and set a timeline
2. Start early. End early. Time is your best friend
3. Work hard. Invest >1000% effort
4. Shoot high, be persistent, and be patient
5. Capitalize on teams and leverage existing strengths
6. Engage the best experts around the country
7. Tell a strong story in a way that anyone can understand
8. Follow a logical flow
9. Be innovative and market your project
10. Conduct pilot studies
11. Know and outline upfront the aim of the main study
12. Conduct secondary analyses of existing cohort studies