Translational Research: What do Grant Reviewers Look for?

Alan M. Delamater, PhD
University of Miami
Miller School of Medicine

Design an Innovative Community-based Study

- Test New Intervention X with patients with health condition Y in a community clinic
- Research participants all have condition Y for at least two years, are between the ages of 21 and 64, can read and write English, and do not have other chronic health conditions or major psychiatric illness
- Intervention X is manualized and consists of 10 sessions delivered over 12 weeks

New Study Design

- Baseline assessments are conducted with reliable and valid measures of symptoms and disease status
- Participants randomized to receive the new intervention X or a usual treatment condition
- Intervention X is delivered by trained research staff
- Post treatment assessment conducted 3, 6, and 12 months post baseline and randomization
- RM ANOVAs to test hypothesis

Strengths of the Study Design

- Well defined patient cohort, with specific inclusion/exclusion criteria
- Standardized intervention with specific objectives in each of 10 sessions
- Trained research staff conducting intervention in community setting
- Randomization to either new intervention or control group

Weaknesses of the Study Design

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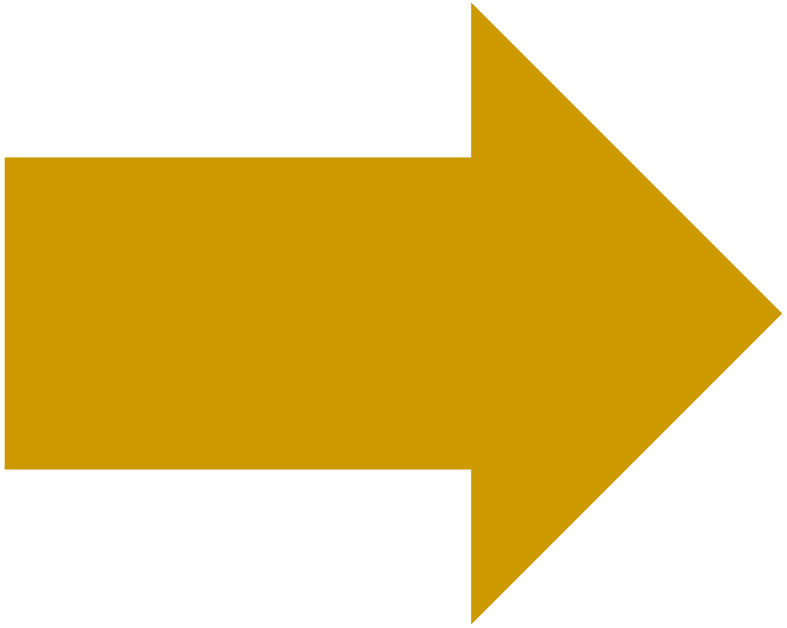
What's Wrong with this Picture?

- Homogenous study sample does not represent real world patients
- Standardized, manualized interventions are not responsive to individual needs of patients with co-morbidities
- University-based trained research staff do not represent community-based clinical staff
- Usual care control groups may not be acceptable to communities
- No measures of cost and quality of life

Bottom Line



- Low External Validity
- Lack of Generalization
- Will Not Be Adopted

Goals of Clinical Research

- Effectiveness of Alternative Treatments
- Mechanisms: Mediators of Treatment Outcome
- Moderators of Treatment Outcome
- Empirical Basis for Clinical Practice

Requirements of Clinical Research

- Homogeneous Samples
- Specification of Variables
- Reliable and Valid Measures
- Standardized Treatment
- Experimental Design
- Statistical Analyses
- Strong Internal Validity
- Designed to test Treatment Efficacy

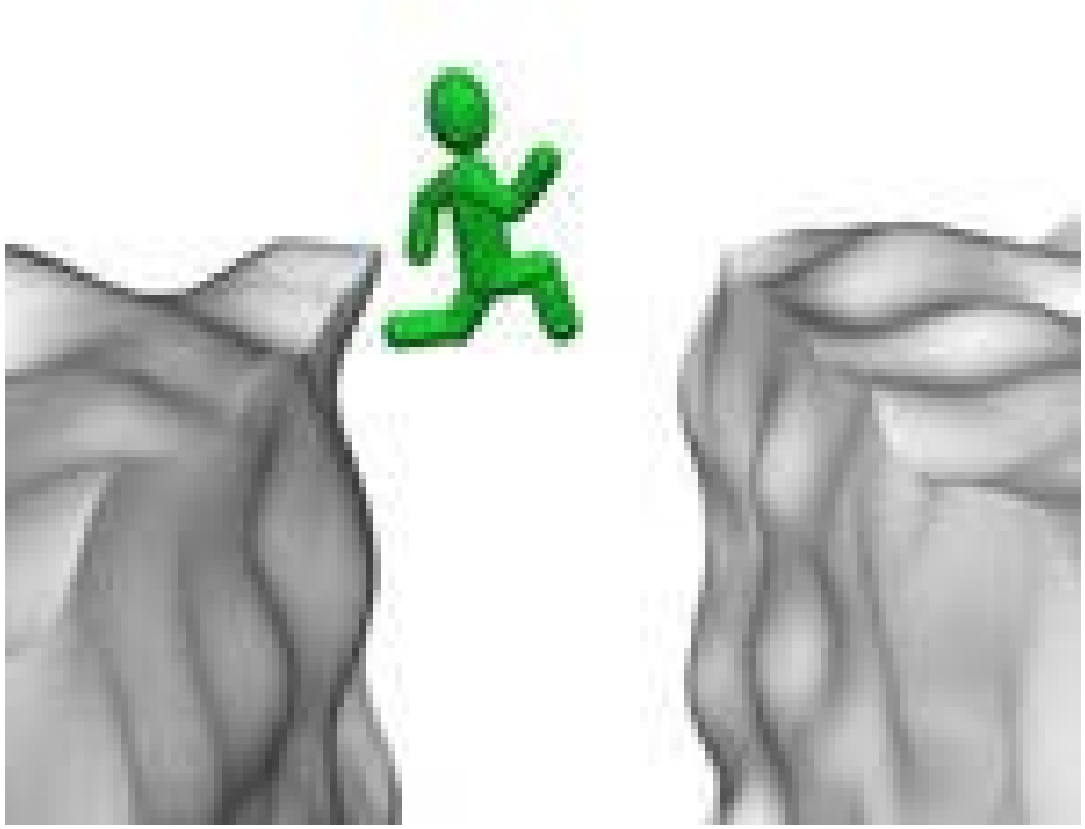
Requirements of Clinical Practice

- Focus on Individual Case
- Individual Tailoring of Treatment
- Flexible Administration
- Evaluation by Clinical Judgment

Gap Between Research and Practice

- In many areas of health care and public health
- Discrepancies between evidence-based, efficacious interventions and what actually occurs in practice have been labeled a “chasm” by the Institute of Medicine
- About half of recommended health care practices are implemented; much less for preventive and health behavior interventions

Clinical Research **Clinical Practice**



Gap between Clinical Practice and Clinical Research

- Types of Disorders
- Types of Treatment
- Duration of Treatment
- Setting
- Involvement of Significant Others
- Perception of Incompatibility between Research and Practice

Failure of Health Research to Translate into Practice

- Barriers to translation include characteristics of :
- Interventions
- Settings
- Research design
- Interactions among these three factors

Interventions

- Efficacious programs may be intensive and demanding for both participants and staff
- High cost and high level of staff expertise required
- Not developed considering user needs
- Not designed to be self-sustaining
- Highly specific to particular setting, not customizable

Settings

- Limited resources, staff time, expertise
- Competing demands, especially among those that serve high risk populations
- Financial/organizational instability
- Program imposed from outside

Research Design

- Not relevant or representative regarding sample of patients, settings, and clinicians
- Failure to evaluate cost, reach, setting adoption
- Failure to assess implementation, maintenance, and sustainability

Interactions Among Intervention, Setting, and Research Design Barriers

- Program reach is low
- Interventions are not flexible
- Interventions not appropriate for target population
- Staffing does not match intervention needs
- Mismatch between organization and intervention philosophies
- Organization unable to implement intervention

Limited Translation of Evidence-based Interventions

- Inadequate training of practitioners
- Lack of funding for practical trials
- Failure to appreciate differences between efficacy and effectiveness, replication and dissemination research
- Failure to consider community perspective in development of interventions and study designs

Community-based Participatory Research (Israel, 1998)

- CBPR improves relevance and effectiveness of public health interventions
- Requires collaborative partnership, involves community partners in all aspects of research
- Builds on strengths and resources of community
- Mutual benefits
- Research team and community interact to bridge gaps between program design and eventual adoption

"Where did the field get the idea that evidence of an intervention's efficacy from carefully controlled trials could be generalized as THE best practice for widely varied populations and settings?"

Green, *Am J Health Behavior*, 2001

Types of Evidence

- Outcome or clinical data
- Theoretical or mechanism data
- Quality of life data
- Feasibility/implementation evidence
- Process or quality of care data
- Quality of improvement data
- Cost and economic data
- Qualitative data
- Internal validity evidence
- External validity evidence

External Validity

- “Inferences about the extent to which a causal relationship holds over variations in persons, settings, treatments, and outcomes”

  - Shadish, Cook, & Campbell (2002)

Types of External Validity Needed to Enhance Translation

- Program Reach and Sample Representativeness: target audience; inclusion and exclusion criteria; participation; representativeness of settings and patients
- Program Implementation and Adaptation: fidelity of treatment; staff training
- Outcomes for Decision-making: significance in relation to clinical guidelines; quality of life; moderators; program intensity; costs
- Maintenance and Institutionalization: long term effects; sustainability; attrition

RE-AIM (re-aim.org)

- Reach
- Efficacy or Effectiveness
- Adoption
- Implementation
- Maintenance and Cost

Efficacy Studies

- **Reach**: homogeneous, motivated samples with few complications
- **Efficacy**: intensive standardized interventions to maximize effect size; RCT designs
- **Adoption**: one setting to reduce variability; many resources
- **Implementation**: done by research staff following protocol
- **Maintenance and cost**: few issues here, focus on individual level

Effectiveness Studies

- **Reach**: broad, heterogeneous, representative samples
- **Effectiveness**: brief feasible interventions not requiring great expertise; adaptable to setting; randomized time series or quasi-exp designs
- **Adoption**: appeal to and work in multiple settings; adapted to fit setting
- **Implementation**: variety of different staff with competing demands; adapted protocols
- **Maintenance and cost**: major issues; setting-level is as important as individual-level maintenance

Disconnect Between Practice and Research

- “The characteristics that cause an intervention to be successful in efficacy research are fundamentally different from and at odds with programs that succeed in population-based effectiveness settings”
  - Glasgow et al., *American J Public Health*, 2003

Disconnect

- “It should not be surprising when the results of an intervention are efficacious under a highly specific set of circumstances but fail to replicate across a wide variety of settings, conditions, and intervention agents in effectiveness research.”
  - Glasgow et al., *American J Public Health*, 2003

The Big Question

- “What are the characteristics of interventions that can a) reach large numbers of people, especially those who can most benefit, b) be broadly adopted by different settings, c) be consistently implemented by different staff members with moderate levels of training and expertise, and d) produce replicable and long-lasting effects (and minimal negative impact) at a reasonable cost?”
  - Glasgow et al., *American J Public Health*, 2003

Translational Research

- Refers to the process by which new science is utilized to improve public health
- Phase I: applies basic discoveries to human healthcare under the controlled conditions of clinical research (efficacy)
- Phase II: promotes the adoption of promising clinical research by community-based healthcare under more uncontrolled conditions (effectiveness)
- Translational research is the ultimate effectiveness test (program evaluations concerned with generalizability)

Practical Clinical and Behavioral Trials

- Provides contextual information to make health research more relevant and aid decision makers to evaluate applicability and generalizability of research
- Heterogeneous and representative samples
- Multiple measures relevant to decision makers (clinical outcomes, cost, quality of life, implementation, adverse effects)
- Comparison conditions relevant to real-world decisions

Focus of Grant Reviewers

- Significance and Impact
- Innovation
- Approach
- Potential for Translation
- Investigator
- Environment
- Recruitment of Women, Minorities, and Children
- Human Subjects
- Budget

Key Points

- Importance of the Issue, Innovation, and Efficacy of the Intervention Approach

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- The intervention approach to be tested must already have a solid empirical basis in efficacy studies.

Key Elements of the Study Approach

- Patients and Setting

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- Process and outcome measures

Patients and Setting

- Targeted to a patient population commonly seen in community settings: diverse and/or high-risk
- Co-morbidities in study sample
- Inclusion and exclusion criteria less stringent than in efficacy studies
- “Real world” clinical setting in the community

Sampling and Randomization

- The sampling and randomization plans must be systematic and well described.
- Will the study sample be representative of the community population?
- Diverse groups of participants are needed to enhance external validity.
- Are the recruitment methods clearly specified and will they be effective?
- What are the plans for retaining subjects for the duration of the study?

The Intervention

- The original intervention should have been well-described, theoretically-based, and innovative.
- Already proven to be efficacious.
- The fundamental intervention approach should have a firm basis in established research.
- Cultural appropriateness

Innovation

- The application of the intervention to be tested for translation would be considered innovative.
- Test novel ways of implementing previously established intervention approaches in real-world settings with diverse or high-risk populations.
- Design and measurement plan

Providing the Intervention

- Who will provide the intervention?
- Research staff (effectiveness study) or existing community agency staff (translation study)?
- Staff training methods should be clearly described, including both the initial and follow-up training.

Design Issues

- Translational research is not the same as clinical trials.
- What is the most appropriate control group or control procedures?
- Besides RCT, consider other appropriate control procedures such as time-series designs, multiple baseline designs, cross-over, quasi-experimental designs.
- Efficacy research typically has more experimental control.

Design Issues

- In effectiveness and translational research, the control group should have ecological validity: e.g., usual care or enhanced clinical care.
- Consideration of mediator and moderator variables
- Plan for measurement of long-term outcomes
- Consideration of potential problems

Statistical Issues

- Statistical expertise on investigative team
- The power analysis should be clearly described and based on real data.
- Will the effect of intervention be clinically meaningful?
- The primary analysis should be an intent-to-treat analysis.
- Specify primary outcomes, secondary outcomes, and mediators and moderators.

Statistical Issues

- Careful documentation needed for number of patients who did not complete the intervention, and reasons for not completing.
- How will missing data be handled?
- Sophisticated models for longitudinal data needed when clinics or teams are randomized (HLM, SEM, GEE, random regression models).
- Link data analysis plan to specific aims; be very specific in your plans.

Process Measures

- Process measures are essential.
- Implementation of the intervention—not necessarily the same as fidelity.
- Costs of providing the intervention (time spent by staff).
- Satisfaction of patients and staff.
- Hypothesized mediators of response to the intervention.
- Barriers to successful implementation should be documented in both the short and long term.

Outcome Measures

- Outcome measures must be reliable, valid, and have clinical utility—if the measurement plan is burdensome, it will increase attrition.
- Measures must be practical in order to be routinely employed in community settings.
- Multi-modal assessment using self-report and objective measures.
- In addition to health outcomes, health behaviors, psychosocial functioning and quality of life should be included as key outcomes in both the short and long-term.

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- Investigative team must have expertise with the intervention and study approach—track record of relevant publications and grants, interdisciplinary team, institutional environment likely to facilitate achievement of study aims.
- Pilot tests in the proposed community setting with the study population necessary to demonstrate the study approach is feasible.

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- To what patient populations and settings will the study findings be expected to generalize to?
- Transferability (application to diverse settings) depends upon well-specified description of the intervention approach (treatment manuals and staff training methods), and evidence that the intervention leads to maintenance of change over long follow-up period—not only for patients but also for the setting.

Bottom-Line

- Does the intervention strategy proposed have the ability to be translated into primary care, community, family or other patient care/support settings?
- Translation requires successful demonstration of the intervention's long-term effectiveness with a diverse patient population in a real-world clinical setting.

Other Reviewer Concerns

- Is the application well-written?
- Is it organized appropriately?
- Is it easily readable?
- Are there typos, spelling errors, missing or incorrect references?
- Are revised applications responsive to the earlier reviews?

Summary of Reviewers' Issues

- Importance of the issue and likely impact.
- Soundness of the approach—recruitment and retention of diverse study sample; type, delivery, and translatability of proposed intervention; measurement of outcome, process, and mediator/moderator variables; use of theory; appropriate design; convincing power analysis and statistical plan.
- Pilot studies to demonstrate feasibility.
- Collaborative arrangements with community-based clinics.
- Experience of the team.
- Ready for "prime time?"

Reviewer Issues

- Reviewers need to be re-socialized—efficacy trials and internal validity vs. effectiveness/translation research and external validity.
- Grant review training for members of study sections and special emphasis panels.

Helpful References

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Integration of Research and Practice