Handbook for Clinical Research
Design, Statistics, and Implementation

Flora M. Hammond, MD • James F. Malec, PhD
Todd G. Nick, PhD • Ralph M. Buschbacher, MD

With over 80 information-packed chapters, Handbook for Clinical Research delivers the practical insights and expert tips necessary for successful research design, analysis, and implementation. Using clear language and an accessible bullet point format, the authors present the knowledge and expertise developed over time and traditionally shared from mentor to mentee and colleague to colleague. Organized for quick access to key topics and replete with practical examples, the book describes a variety of research designs and statistical methods and explains how to choose the best design for a particular project. Research implementation, including regulatory issues and grant writing, is also covered.

The book opens with a section on the basics of research design, discussing the many ways in which studies can be organized, executed, and evaluated. The second section is devoted to statistics; it explains how to choose the correct statistical approach and reviews the varieties of data types, descriptive and inferential statistics, methods for demonstrating associations, hypothesis testing and prediction, specialized methods, and considerations in epidemiological studies and measure construction. The third section covers implementation, including how to develop a grant application step by step, the project budget, and the nuts and bolts of the timely and successful completion of a research project and documentation of findings: procedural manuals and case report forms; collecting, managing and securing data; operational structure and ongoing monitoring and evaluation; and ethical and regulatory concerns in research with human subjects.

With a concise presentation of the essentials for successful research, the Handbook for Clinical Research is a valuable addition to the library of any student, researcher, professional, or clinician interested in expanding the knowledge base of his or her field.

Key Features:
■ Delivers the essential elements, practical insights, and trade secrets for ensuring successful research design, analysis, and implementation
■ Presents the nuts and bolts of statistical analysis
■ Organized for quick access to a wealth of information
■ Replete with practical examples of successful research designs—from single case designs to meta-analysis—and how to achieve them
■ Addresses research implementation including regulatory issues and grant writing

Recommended Shelving Category: Medical
Handbook for Clinical Research
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This is a sample from HANDBOOK FOR CLINICAL RESEARCH: DESIGN, STATISTICS, AND IMPLEMENTATION

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And so, the *Handbook for Clinical Research: Design, Statistics, and Implementation* took shape. Part I covers the basics of research design: the variety of ways in which studies can be organized to address questions of association or causation; the appropriate sequencing of studies in a particular area to move most efficiently from demonstration of concept to a definitive and rigorous trial; methods and appropriate rigor of control conditions; retrospective and prospective trials; qualitative and quantitative analyses; and methods for summarizing, evaluating, and reporting clinical research in a particular area. Part II, statistics, begins with a discussion of selecting the correct statistical approach and when to consult a statistician. Part II then reviews the varieties of data types; descriptive and inferential statistics; methods for demonstrating associations, hypothesis testing, and prediction; specialized methods, such as survival modeling; and specialized methods for epidemiological studies and measure construction. Part III, implementation, begins with a number of chapters on developing successful grant applications from planning and seeking consumer input to developing specific sections of research grant proposals, the project budget, and ancillary materials. The final chapters of this section cover the nuts and bolts of the timely and successful completion of the research project; developing procedural manuals and case report forms; collecting, managing, and securing data; operational structure and ongoing monitoring and evaluation of the project; and ethical and regulatory concerns in research with human subjects.

Many of the authors (including ourselves) at first found the succinct, focused format of the book to be a quick reference guide for clinical researchers in any discipline—a book that could assist them in their daily work planning and conducting research studies, journal and grant reviews, and mentoring. We began to imagine a book that might serve as a supplementary text to courses on research design and analysis as well as grant writing courses and workshops, or that might be a good primary text on research for any clinical training program with a clinical research component.
be challenging. Most of us would have found it easier to write the traditional 30-odd-page chapter replete with extensive referencing and interesting (at least to us) intellectual alleyways. However, all of the authors rose to the challenge and boiled down their insights in each topic area to the key elements, practical considerations, potential pitfalls, and helpful hints that this text was designed to communicate. Chapters include a few references for those seeking a more in-depth treatment of the topic area.

Our hope in assembling this cogent overview of the broad realm of clinical research is to provide a text that both established and apprentice clinical researchers will find to be a useful guide and reference.

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Design
DEFINITIONS AND DESCRIPTIONS

■ Active ingredients: The components of an intervention under study that produce the therapeutic change according to its underlying theoretical model.
■ Enablement/disablement theory: A class of theories about how changes in a proximal clinical target (referred to as the target of treatment) will influence distal clinical targets (referred to as treatment aims).
■ Target of treatment: The functional variable, that is, hypothesized to be directly changed by the treatment (eg, if leg strengthening exercises are performed in the hope that ambulation will be improved, “leg strength” is the target of treatment; improvement in ambulation depends on many factors beyond the treatment, as specified by enablement/disablement theory).
■ Treatment aim(s): Treatment goals that are distal to the target(s) of treatment, and that are intended to be indirectly improved, via mechanisms specified by enablement/disablement theory (eg, ambulation in the above example).
■ Treatment fidelity: The extent to which a study intervention is being carried out as it was intended in the protocol or manual (ie, that the specified active ingredients are being delivered) and is clearly differentiable from control intervention (eg, in a pilot or confirmatory randomized controlled trial [RCT]).
■ Feasibility: Demonstration that “moving parts” of a clinical trial work (eg, recruitment, retention, measurement reliability, and fidelity of the therapists to the intervention).
■ Proof of concept proof of principle: Evidence supporting the treatment theory (theory of the mechanism of action by which the delivered “active ingredients” of treatment produce change in an aspect of functioning).
■ Minimum clinically important difference (MCID): The minimal effect that has clinical relevance in the management of patients.

INTRODUCTION

■ Imagine a researcher wishing to develop an entirely new therapeutic intervention or treatment, or to adapt an existing treatment for a new population. This chapter describes the work needed prior to testing this new treatment in an adequately powered RCT or other rigorous confirmatory design. This chapter distinguishes treatment development research from treatment testing research.
■ Treatment development: The work needed prior to doing a well-powered RCT or other rigorous confirmatory trial. Treatment development includes:
  ■ Observational studies of the condition of interest in the absence of specific treatment (or in the context of failure to respond adequately to an established treatment) may help to define the state of affairs to be improved upon and to identify the sites and time frames most suitable for subsequent research.
Theory development, open-label studies, small-pilot RCTs, and treatment manual development.

All stages from the initial conceptualization and protocollization of a new treatment, to the pilot work done to demonstrate the feasibility of a treatment study.

Treatment testing refers to studies large enough to be considered definitive tests of a treatment hypothesis. Typically, these are well-powered RCTs, often multicentered, but may include rigorous quasi-experimental designs. Treatment testing can be further divided into confirmatory testing of the treatment theory and testing of the practical clinical impact of the treatment.

In some cases, these goals can be combined—when the target of treatment is also a clinically relevant aim of treatment (eg, when strengthening exercises are performed so that heavier items can be lifted, the target of “increased strength” is a clinical goal in its own right).

In other cases, the best possible treatment of the target may not lead to distal functional improvements in all patients, as when a patient with leg weakness and ataxia fails to improve in ambulation (an aim) despite strengthening exercises that improve the weakness (the target). In such cases, one may perform a confirmatory trial demonstrating that the treatment reliably improves weakness (the target), but one must assess its practical impact on ambulation in a separate research with a very different design (see below).

Confirmatory testing of the treatment theory

 Confirmatory tests of a treatment theory should rigorously compare the effects of the treatment versus some comparator on measured changes in the treatment target (efficacy in treating the target).

Later tests may explore whether those treatment-induced changes in the target are reliable across a heterogeneous population of patients, and when delivered by heterogeneous clinicians (effectiveness in treating the target).

Testing of the practical clinical impact of treatment

 When testing for practical impact on a distal clinical aim (eg, participation in social or role activities), one must have an enablement/disablement model in mind of how the treatment target relates to the distal aim, and what other strengths and limitations may also affect the aim.

Enhancing treatment impact on a distal clinical aim requires either:

1. Identifying patients for whom the target is the primary limitation with respect to the aim (eg, patients whose main obstacle to ambulation is weakness); or

2. Developing a “package” of treatments that address the multiple potential targets that limit performance of the aim.

Research to flesh out the enablement/disablement model of a particular functional aim area need not be carried out for each treatment separately, that is, the cause of the change in the target (ie, what treatment produced it) is not relevant to how that change will affect distal aims.

IMPLICATIONS

Treatment development is a critical step in getting to evidence-based rehabilitative treatment.

Treatment development consists of three key steps:

- Step 1: Manualization or protocollization of the intervention;
- Step 2: Conducting iterative case series, often called an open-label trial, to test and modify both the intervention and all aspects (such as inclusion criteria, outcome measures) of the research;
- Step 3: Conducting a pilot RCT to demonstrate feasibility of doing an RCT.

Treatment development is required prior to treatment testing.

- One key goal of treatment development research is to reduce the chances of failure (to demonstrate efficacy, or effectiveness, of a promising treatment) at the confirmatory RCT level.

A “negative result” is interpreted to mean that the underlying treatment theory is false. However, a negative result may also occur when the treatment theory is correct but one of the following failures occurred:

- Treatment is given in an inadequate dose.
- Treatment dose/duration is adequate to be potent, but is poorly implemented by study clinicians (ie, poor treatment fidelity).
- Treatment implementation by clinicians is adequate, but patient adherence too low.
- Patient adherence to treatment is adequate, but missing data rate is too high (due to patient dropout/refusal or other reasons).
- Recruitment is poor, leading to inadequate sample size.
Treatment Development

Step 1: Treatment manual development
- Multidisciplinary team with expertise in treatment development
- Identify the “active ingredients”
- Create a treatment manual that specifies active ingredients
- The manual needs to accomplish two important things
  - Implement the underlying treatment theory
    - For example, if the researcher is testing a theory regarding treatment of working memory, the manual should address working memory and the specific “ingredients” required to modify it.
    - Be practical for use by the clinicians who are doing the intervention in the study. Clinicians who provide the treatment need to learn how to provide the treatment consistently and do not necessarily need an extensive description of the underlying theory.
- Cannot manualize every aspect of a treatment
  - Decide what are the “essential ingredients” or mechanisms of an intervention, according to the theory that is being promoted.
  - Some manuals are highly protocolized, while others are much less so.
    - Typically in the evolution of a new treatment intervention, the manual starts out brief, then gets more extensive and more protocolized (often with case examples) as the researchers get more experienced with the active ingredients, and then finally gets shorter and less protocolized in efforts to make the treatment implementable in the real world.
- Manuals range from descriptions of a treatment “approach” to step-by-step “how to” manuals, with tradeoffs.
  - The former allows more flexibility in tailoring to individual patients, but provides less specific guidance about exactly what the clinician should do in specific situations.
  - Especially in the early phases of treatment development, a manual is an evolving document.
- Review and make changes based on advice and information from collaborators:
  - The study clinicians who are implementing the intervention
  - Debriefing patients involved in early treatment delivery
- Query these individuals about what is feasible:
  - How much supervision of implementers is needed, and how will it be done?
  - What is likely to be well/poorly received by the patients?
- Feedback from patients, their families, and providers is very helpful at this stage of treatment development, and increasingly is recommended or even required in grant applications (eg, Patient-Centered Outcomes Research Institute—PCORI—applications).
The treatment manual development step is usually fairly brief but continued evolution of the manual is likely in ensuing phases.

In particular, if early treatment testing suggests limited potency, the treatment may need to be revised, and with it the manual.

**Step 2: Conduct iterative case series**

- The iterative cases series is similar to “Phase 1” in drug treatment (Phase 1, Phase 2, and Phase 3) parlance.
- Probably the most important step because it is the main opportunity to gain experience with the intervention and with the research methods, and to make changes.
- In treatments for rapidly evolving conditions (eg, during rapid natural recovery from a neurologic event), case series, although useful for exploring feasibility issues, may provide little evidence regarding proof of principle, requiring introduction of more rigorous control conditions earlier in the treatment development process.
- Oftentimes this phase starts with wide inclusion and (few) exclusion criteria.
  - Fine-tune these based on experience in this phase; for example, the observation that patients within a certain subgroup (defined by demographics or clinical presentation) are particularly good, or particularly poor, subjects for this intervention.
- Treat all participants (no control group), unless a control group is required to assess proof of concept.
- Keep tweaking intervention based on observations of where it appears to be inadequate.
- Gather feasibility and validity data on all measures.
- Supervise study clinicians implementing the treatment.
  - Often, and particularly early in this stage, the research team will need to directly observe all of the treatment sessions.
  - Provide feedback to implementing clinicians regarding what is being done well and what needs to change in order to achieve good treatment fidelity.
- Measure fidelity.
  - It is often advisable to verify that the control treatment is lacking in the treatment’s active ingredients, even prior to a pilot RCT stage.
  - Fidelity assessment should focus on the essential ingredients of the theory underlying the new intervention.
  - In research treatment development and testing, the following treatment fidelity steps should be implemented, documented, and detailed in publications of the research:
    - Treatment manual that defines treatment
    - Details of training of therapists in the treatment
    - Details of supervision of therapists
    - Fidelity monitored by external referees
    - Fidelity data reported
    - High level of fidelity attained and maintained in RCT
- Measure processes (ie, observable mechanisms) when possible.
- The case series step is complete once the researchers can see, consistently and to their satisfaction, that the research methodology is feasible, and that the intervention seems to be working:
  - Implementing clinicians carry out the intervention with high fidelity.
  - Research methods for recruitment, retention, measurement, and adherence are adequate.
  - Participants have a good treatment outcome (and outcome measures can detect this).
- The main limitation of a case series is that participants may appear to do well because of naturalistic change, expectancy, or measurement error. Thus, it is quite possible to gain a false sense of confidence regarding feasibility and proof of concept during a case series, which is then “lost” during a pilot RCT (because the control group shows similar change).

**Step 3: Pilot RCT**

- Pilot RCT is a randomized comparison of experimental intervention to a comparator.
- Usually a necessary step in treatment development, if the ensuing step is a confirmatory (well-powered) RCT. However, many of the principles below hold for other (quasi-experimental) designs.
- Uses measures of change in the treatment target as the primary criterion for assessing proof of principle.
- The goals of a pilot RCT are:
  - To confirm feasibility as demonstrated by:
    - Good recruitment and retention
    - Even though recruitment and retention for treatment may have been adequate in the case series, introduction of blinding or randomization may lead to a drop in recruitment or retention that must be anticipated and corrected.
    - Comparator treatment is satisfactory (eg, no excessive dropout, includes no active treatment elements)
    - Outcome and process measures are practical, reliable, and responsive

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Satisfactory treatment fidelity:
- High adherence and competence in the active group
- Effect of active treatment on treatment target is clearly distinct from the control intervention
- Demonstrate proof of concept as described above but not to confirm efficacy or effectiveness of the intervention.

A successful pilot RCT shows readiness for a confirmatory RCT.
- It is generally not expected to show a statistically significant effect, and it should not be used either to report that a new intervention has been “shown to be effective.”
- Additionally, the effect size in a pilot RCT may not provide an accurate estimate for powering future confirmatory studies (because the confidence interval of the effect size in a small study is often large, and because effect sizes in pilot RCTs tend to be overly optimistic).
- Instead, the MCID should be considered in determining sample size in future studies (see Chuang-Stein et al., 2011).
- The appropriate method for determining the MCID, however, remains controversial (see Revicki et al., 2008).
- The pilot RCT, as well as the case series, are publishable findings.
- However, they should be reported not as efficacy tests but rather as preliminary, feasibility, treatment development, or proof-of-concept studies.
- The vast majority of intervention studies in medicine are pilot studies (but are often not identified as such in publications).

The pilot RCT stage is also the last chance to adjust various components of the intervention or other aspects of the research methods (such as inclusion/exclusion criteria or analytic strategy), as confirmatory RCTs usually “lock in” all design decisions at the beginning of the study.

Although it is not always necessary to do a pilot RCT prior to a confirmatory RCT, a pilot RCT is necessary when:
- Recruitment (and retention) in randomized treatments is uncertain.
- Feasibility/credibility of comparator condition in the study population is unknown.
- The study team (or the research community) has little research experience with either the experimental intervention or with randomized tests of it.
- In a competitive funding environment, presenting pilot data demonstrating feasibility and a possible treatment effect may enhance the chances of funding.

Confirmatory Testing of the Treatment Theory (Efficacy Testing)

Design protocol for RCT or appropriate rigorous study design
- Determine necessary sample size for adequate statistical power to test both positive and negative results with respect to the primary outcome(s). Determine statistical analysis that will be used for the main confirmatory analysis.
- Identify any a priori hypotheses about subgroup differences in response to treatment, since only pre-specified subgroup analyses are likely to be trusted as confirmed findings, rather than hypotheses for future exploration.
- Develop standardized approaches to training of treaters, assessment of fidelity, recruitment and retention, and data quality.
- Conduct regular surveillance of enrollment, fidelity, and data quality throughout the trial.
- Conduct the pre-specified analyses when the trial is complete.

Testing the Practical Impact of Treatment (Effectiveness Testing)

Once a treatment has been confirmed to produce robust impact on the target of treatment, consider enablement/disablement models of the functional domain to understand the relationship between the treated target and other related areas of real world function. What kinds of distal impacts are plausible given these models?

Design subsequent studies that:
- Explore distal impact in patients with impairment limited to the treated target (who should have distal benefit).
- Explore distal impact in patients with multiple impairments who receive a “package” of treatments that address multiple relevant targets.

PITFALLS

A new treatment may potentially fail or be suboptimal at any of these steps. Although this sometimes requires abandoning the treatment theory, in many cases it requires going back a step or two in the treatment development stages, and repeating steps.

Step 2 (iterative case series) is often the most important part of treatment development but also the hardest to get buy-in from grant or journal...
reviewers (who prefer to see an RCT design). In grant applications, it is important to clearly explain the critical role of the proposed case series in the planned stages of the specific new treatment development.

- Treatment fidelity measurement is nonnative to some clinical fields, and attaining and demonstrating good treatment fidelity may be a novel skill set for researchers. See Hildebrand et al (2012) for an empirical example of this process.
- See Whyte and Barrett (2012), for a more detailed description of the stages of rehabilitation treatment development and their pitfalls.

HELPFUL HINTS

- Each of the various treatment development phases is essential. Do not skip or speed through steps.
- Get help from experts in treatment research.
- Ensure adequacy of measurement (completion, reliability/validity, and sensitivity to change) before moving to RCT phases.

SUGGESTED READINGS


