The Myth of Randomized Experiments as the Gold Standard when Researching Comparative Effectiveness

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Introduction

With many different forms of radiation therapy available for the treatment of cancer, it becomes essential to methodologically compare the effectiveness of each type of intervention. However, many stakeholders are insisting upon the experimental model of a randomized controlled trial (RCT) in order to adequately compare outcomes from varying treatment modalities. This design is unnecessary and often impractical to execute in a real-world setting. With patients actively seeking out their preferred form of treatment, it can be difficult to enroll a study designed to randomize patients to various forms of therapy.

Randomized controlled trials are developed to compare an experimental group to a control group in order to determine efficacy. Various forms of radiation (ex: photons, brachytherapy, protons, etc) can be used to treat cancer and are not considered experimental. Therefore, since no arm of the study will be truly experimental, this study design is not necessary. This type of research is also not appropriate when attempting to research comparative effectiveness and focusing on striving to attain the strict standards of this model can delay forward scientific progress.

Methods

For comparative effectiveness research, data already generated from existing clinical research or new evidence of the effectiveness of a health-care service is utilized. Data from each type of treatment modality is then compared to determine benefits and harms. These pragmatic trials measure effectiveness- the benefit of treatment in a real world setting, not efficacy- whether or not the treatment works.

RCTs vs Pragmatic Research

RCT	• Focus on ***efficacy*** • Stringent inclusion/exclusion criteria make it difficult to investigate a treatment across heterogeneous participant groups • Strict rules of treatment, including the need for a control or sham treatment • Best suited in situations where blinding of patients and practitioners is possible • Most RCT's are performed in academic arenas or in large clinical trail centers, in a controlled, experimental setting • "On treatment" analysis can introduce bias which overestimates the benefit of treatment
Pragmatic	• Focus on ***effectiveness*** • Testing a treatment in normal clinical conditions allows for more variability and inclusion of patients who may otherwise never be treated in an RCT (older, younger, pregnant) • Treatment can be tailored to individual patients, often a control or placebo is not needed • Most useful when blinding is not possible. Bias of clinicians and patients is accepted as a normal occurrence in the clinical environment • Pragmatic trials can be performed in routine clinical environment • "Intention to Treat" analysis helps reduce overestimation bias, and as such the ITT approach has also been used in many RCT designs

Conclusion

Randomized controlled trials often lack external validity: meaning the results are not necessarily translatable to the general population being studied. With <10% of cancer patients participating in clinical trials, comparative effectiveness can better utilize patient data to address specific research questions that arise from radiation therapy stakeholders.

When policy makers and payers insist upon using data solely from RCTs, this creates ethical dilemmas: One being that the patient might feel coerced into study participation to ensure treatment coverage, and two being that true research equipoise might not exist among the possible randomly assigned study arms. RCTs can also promote selection bias whereas the pragmatic studies generally allow for data to be analyzed from a wide array of real-world patients treated in various settings with various co morbidities, which allows for generalizable results.

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