Ethical Considerations in Conducting Pragmatic Trials in Oncology

Marilyn J. Hammer, PhD, DC, RN

Pragmatic trials evaluate interventions in real-life scenarios, which differ from explanatory trials that control for numerous factors and variables to best determine causal associations. Each approach has advantages and disadvantages. Conducting pragmatic research trials while maintaining the tenets of the ethical conduct of research can sometimes be challenging, particularly regarding informed consent. In this column, distinctions between pragmatic and explanatory trials are discussed from an ethical view.

Hammer is the director of research and evidence-based practice in the Department of Nursing at Mount Sinai Hospital in New York, NY.

No financial relationships to disclose.

Hammer can be reached at marilyn.hammer@mountsinai.org, with copy to editor at ONFEditor@ons.org.

Keywords: research; pragmatic and explanatory trials; ethics

ONF, 44(5), 537–539.

doi: 10.1188/17.ONF.537-539

Pragmatic trials capture the essence of an intervention in real-life scenarios and time, and may differ from explanatory trials, which focus on the efficacy of an intervention via ideal clinically orchestrated methods (Gaglio, Phillips, Heurtin-Roberts, Sanchez, & Glasgow, 2014; Schwartz & Lellouch, 2009). Schwartz and Lellouch (2009) defined pragmatic trials as analyzing outcomes of interventions between subjects who choose which intervention to participate in. In comparison, explanatory trials test causal associations or the efficacy of an intervention under controlled conditions (Gaglio et al., 2014; Schwartz & Lellouch, 2009; Thorpe et al., 2009). Pragmatic trials can also take the form of randomized, controlled trials, which compare a new therapy to standards of care (Kalkman, van Thiel, van der Graaf, et al., 2017; McKinney et al., 2015). Pragmatic trials usually have larger samples, occur in varied settings, and boast high external validity, whereas explanatory trials are more controlled, have smaller samples, and claim higher internal validity (Patsopoulos, 2011).

Research ethics can sometimes be challenging to uphold when conducting pragmatic trials. By defining the constraints of the research protocol according to ethical guidelines, the natural setting of the pragmatic trial can be compromised. For example, the process of obtaining informed consent with forms that must include specific criteria can disclose information to participants that could compromise the study, or, in some cases, the trial can be compromised by the participants knowing they are part of the study (McKinney et al., 2015). In addition, the informed consent content and process can lead to a biased sample because of select groups who agree to participate and who may not be a comprehensive representation of the targeted population (Kalkman, van Thiel, Zuidgeest, et al., 2017), therefore limiting external validity (Patsopoulos, 2011). A growing argument among researchers conducting pragmatic trials is for the use of alternate consents, such as integrated consent (a combined consent process for clinical procedures and research), broadcast consent (notifications about trials are distributed, and patients are given the opportunity to ask questions; no written informed consent exists), or complete waivers of consent (Kalkman, van Thiel, Zuidgeest, et al., 2017). Another approach gaining popularity is staged-informed consent, in which individuals within a cohort sign one consent to be randomized to a trial, and those randomized to the intervention arm are given a second consent that details the intervention (therefore reducing crossover and contamination from those not randomized to the intervention). At the end of the study, the entire cohort receives the

aggregate study findings (Young-Afat et al., 2016).

Conducting pragmatic trials using these new informed consent approaches is promising (albeit potentially controversial) for increasing the depth and breadth of research findings at accelerated rates. There is a delicate and sometimes precarious balance to maintain between answering the research question for the good of humankind and, in the process, ensuring that the research is ethically sound. In addition, as researchers are designing the study, selecting between a pragmatic or explanatory method may be unclear. One tool designed for this purpose is the pragmatic-explanatory continuum indicator summary (PRECIS), which guides researchers to the best method through addressing specific questions within 10 targeted domains (Thorpe et al., 2009).

Guidelines aside, the lines between pragmatic and explanatory trials may be blurred. To capture the differences, the following research study example has been provided, which will delineate the differences between a pragmatic and exploratory study. Included are implications for the ethical conduct of research.

Research Study Example

Many pragmatic trials focus on testing pharmacologic agents in mostly phase 4 trials (Patsopoulos, 2011); however, to simplify the comparison between methods, this study example outlines a yoga intervention for stress reduction among patients undergoing treatment for cancer. The study includes an intervention group participating in a yoga activity and a control group continuing with their regular activities. Both groups complete stress questionnaires, and saliva samples are collected to measure cortisol levels. The first three patients interested in participating are patient XX (a woman with breast cancer), patient XY (a man with lung cancer), and patient XY-X (a genetic male, phenotypic female with colon cancer).

Explanatory Study Design

Patients undergoing treatment for solid tumor cancers at a large urban cancer center were targeted for the study. Flyers highlighting yoga for stress control were posted in the waiting areas of the cancer center, prompting patients to ask members of the healthcare team about the study. Those expressing interest met with a member of the study team, were screened for eligibility, signed a consent form, were randomized into the study arm or control group, and were given the stress questionnaire, saliva collection tubes, and instructions with specific times in the morning to collect the saliva samples. Patients XX and XY were enrolled in the study. Patient XY-X was not enrolled because she was taking estrogen therapy, which was thought to alter cortisol expression (Edwards & Mills, 2008). Those in the yoga group were scheduled for their first yoga session with other patients in the study. Three months after enrollment, patients were given another questionnaire asking about their normal routines, including what activities they participated in during the past three months. Those in the yoga study arm were given a brief survey about the yoga class.

Pragmatic Study Design

Patients undergoing treatment for solid tumor cancers at a large urban cancer center were targeted for the study. Flyers highlighting a study about stress were posted in the waiting areas of the cancer center, prompting patients to ask members of the healthcare team about the study. The institutional review board granted an integrated consent, allowing patients to agree to participate in the study while consenting for clinical care. Patients XX, XY, and XY-X all were included in the study, and they were not informed that the researchers were interested in the effects of yoga on stress. Patients were given the stress questionnaire, saliva collection tubes, and instructions to collect saliva when they woke up in the morning. Three months after enrollment, patients were given another questionnaire asking about their normal routines, including what activities they participated in during the past three months. Those who participated in yoga were compared to those who did not.

Benefits and Limitations

The benefits of the explanatory study design were the controlled environment of the yoga intervention, the specific timing of the saliva sample collections for cortisol analysis (it is important to control for alterations because of the circadian rhythm [Straub & Cutolo, 2016]), ensuring enrollment of a relatively homogenous sample, and following stringent guidelines of research ethics. This study design boasted strong internal validity and was able to show a causal inverse association between yoga and stress. Limitations of this study design were decreased external validity; a potential confounding variable of an all-patient yoga group, which may have also served as a support group that could also alleviate stress; and the challenge of sustainability.

The benefits of the pragmatic design were the natural selection and setting of patients practicing yoga, patients not being encumbered with having to wake up within a certain time frame in the morning for the saliva collection, a faster enrollment process by use of integrated consent, a more diverse sample with strong external

validity, and strong sustainability among patients whose usual practice is yoga. The limitations included poor internal validity (e.g., various forms and settings of yoga practice, various times and frequency of yoga, altered cortisol findings related to a lack of collection time constraints, lack of strict inclusion and exclusion criteria) and the inability to assess a causal association between yoga and stress.

Research Ethics

Ethically, both methods maintained patient autonomy with the patient choosing whether or not to enroll. Considering beneficence, the explanatory trial could show that the benefits of yoga outweigh the harms. Similarly, in terms of nonmaleficence, patients were screened for the safety of the intervention and their ability to participate in yoga with healthcare team members on hand in case any adverse events occurred during yoga practice. In terms of justice, however, the explanatory trial was restrictive and not available to all. The pragmatic trial could show beneficence in a global sense but not a specific one, and no protective mechanisms were in place for those who may have experienced an adverse event during yoga. However, patients may participate in many activities outside of trials that researchers and clinicians cannot control (including deleterious behaviors, such as smoking). The pragmatic trial allowed for the involvement of a diverse, heterogenous sample, addressing the ethical principle of justice.

Conclusion

Pragmatic trials in oncology have many advantages, particularly investigating patients with cancer as they undergo treatment in real life. More controlled explanatory trials are advantageous in lending greater insights into cause and effect and better understanding of molecular mechanisms, and ensuring that tight ethical guidelines are maintained. What may be missing, however, are some of the influences of natural life on those molecular mechanisms and, with that, broader generalizability. Viewing pragmatic and explanatory trials as a continuum is highly appealing when the specific study questions are conceptualized. As the momentum continues for faster answers to study questions, more inclusivity of patient input, and reaching more diverse populations, pragmatic study designs are likely to become more prominent in the conduct of research and dissemination in the scientific literature.

References

Edwards, K.M., & Mills, P.J. (2008). Effects of estrogen versus estrogen and progesterone on cortisol and interleukin-6. *Maturitas, 61,* 330–333.

Gaglio, B., Phillips, S.M., Heurtin-Roberts, S., Sanchez, M.A., & Glasgow, R.E. (2014). How pragmatic is it? Lessons learned using PRECIS and RE-AIM for determining pragmatic characteristics of research. *Implementation Science, 9,* 96. doi:10.1186/s13012-014-0096-x

Kalkman, S., van Thiel, G., van der Graaf, R., Zuidgeest, M., Goetz, I., Grobbee, D., & van Delden, J. (2017). The social value of pragmatic trials. *Bioethics, 31,* 136–143. doi:10.1111/bioe.12315

Kalkman, S., van Thiel, G.J.M.W., Zuidgeest, M.G.P., Goetz, I., Pfeiffer, B.M., Grobbee, D.E., & van Delden, J.J.M. (2017). Challenges of informed consent for pragmatic trials. *Journal of Clinical Epidemiology* [Advance online publication]. doi:10.1016/j.jclinepi.2017.03.019

McKinney, R.E., Jr., Beskow, L.M., Ford, D.E., Lantos, J.D., McCall, J., Patrick-Lake, B., . . . Weinfurt, K. (2015). Use of altered informed consent in pragmatic clinical research. *Clinical Trials, 12,* 494–502. doi:10.1177/1740774515597688

Patsopoulos, N.A. (2011). A pragmatic view on pragmatic trials. *Dialogues in Clinical Neuroscience, 13,* 217–224.

Schwartz, D., & Lellouch, J. (2009). Explanatory and pragmatic attitudes in therapeutical trials. *Journal of Clinical Epidemiology, 62,* 499–505. doi:10.1016/j.jclinepi.2009.01.012

Straub, R.H., & Cutolo, M. (2016). Glucocorticoids and chronic inflammation. *Rheumatology, 55*(Suppl. 2), ii6–ii14. doi:10.1093/rheumatology/kew348

Thorpe, K.E., Zwarenstein, M., Oxman, A.D., Treweek, S., Furberg, C.D., Altman, D.G., . . . Chalkidou, K. (2009). A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. *Journal of Clinical Epidemiology, 62,* 464–475. doi:10.1016/j.jclinepi.2008.12.011

Young-Afat, D.A., Verkooijen, H.A.M., van Gils, C.H., van der Velden, J.M., Burbach, J.P., Elias, S.G., . . . van der Graaf, R. (2016). Brief report: Staged-informed consent in the cohort multiple randomized controlled trial. *Epidemiology, 27,* 389–392. doi:10.1097/ede.0000000000000435