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ETHICS IN CONVERSATION

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Ethical Challenges in the Medical Practice and in the Regulation of New Cancer Therapies: A Christian's Perspective

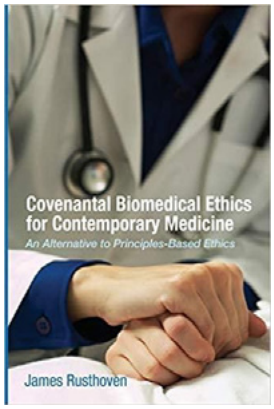
James J. Rusthoven, MD, PhD

Dr Jim Rusthoven is a distinguished Canadian oncologist, and also has a PhD in theology and bioethics, published as Covenantal Biomedical Ethics for Contemporary Medicine: An Alternative to Principles-Based Ethics (Eugene, OR: Pickwick, 2014). Jim thus combines professional and theological expertise, an invaluable combination. Jim is an Associate Fellow of KLC. 2020 was the two hundredth centenary of Florence Nightingale's birth. It has also been a year in which the role of medicine has been indispensable. Thus, we are delighted to publish this piece from Jim.

- Craig Bartholomew

Introduction

I was called by our Lord to train for and engage in the practice of medicine. Equipped with a basic understanding of a Christian Reformational worldview in my undergraduate experience, I went through medical 'basic training' and eventually completed training as a cancer specialist (more specifically, a medical oncologist). After working in a position that involved teaching medical trainees, conducting clinical research and engaging in clinical practice, I took a position as senior clinical researcher with a large pharmaceutical company, in large part to understand new drug development 'from the inside' as well as cultivating a growing interest in clinical research ethics. After several years of direct exposure to ethical challenges in new drug development, I felt called to graduate studies, through which experience I developed a foundational, Reformed critique of the predominant, minimalist bioethical framework known as principles-based ethics. Out of concern for the emphasis of the latter on consensus and an ethical decision-making process over against morally authoritative grounding, I set out to open up a covenantal ethical framework built on earlier work of other Reformed Christian bioethicists. Through the spectacles of a Reformational worldview, it became evident to me that such a framework might better help health care professionals of various types develop ethical practices rooted in their relationships with co-workers, patients and others involved in health care.



A Reformational Worldview of the Created Order

Initially developed and promoted over a century ago by Christian statesman, philosopher and theologian

Abraham Kuyper and further developed decades later by Christian philosopher Herman Dooyeweerd and others, this worldview envisions the entire cosmos as created, ordered and maintained by God. These Reformed thinkers see the importance of distinct aspects or dimensions of life, including all dimensions of vocational pursuits, as truly thriving only under the rule of Christ as creator and Lord of our world. Dooyeweerd empirically recognizes a world composed of irreducible dimensions, also understood as ways of being or functioning aspects. Through this vision, he sought to resist attempts by many scientists and professionals in particular to reduce the richness of God's creation to only certain, largely more quantifiable aspects. In this Reformational worldview, each dimension is distinct from the others, yet closely interacts with the others in everyday life. In medicine, for example, the numerical data from diagnostic testing or efficacy measurements in clinical trials are only meaningful indicators of patient well-being when understood in the context of the clinical (physical, biotic, psychological, etc.) manifestations of illness in patients. Similarly, new and effective drugs should be developed, and their marketing driven, primarily by the ethical dimension or aspect to improve human health and flourishing, yet they are usually developed and promoted by manufacturers primarily to satisfy the profit expectations of their shareholders.

From this perspective, human relationships also express these dimensions, each type of relationship defined and activity directed by a particular dimension. For example, in church communities, human relationships are expressed primarily through the guiding dimension of faith in God. By contrast, profit-making business corporations encompass their relationships internally and those with customers ultimately by the economic dimension of profit for their shareholders.

Medical Practice

Consequently, as seen through a Reformational worldview, in the clinical practice of medicine the *ethical* dimension focuses and directs the other multiple dimensions of relational activity in the practice toward its primary goal of addressing the medical needs of patients.[1] [2] Some have used the term 'ethic of care' to capture the basis of the caregiver-patient relationship. As in other relationships, dimensions or aspects in clinical practice interact, some coming to prominence at different times in a practice. For example, the social dimension is best served through optimal communication between patients and various caregivers engaged in the practice. The logical dimension can well serve the relationship through well-thought-out, evidence-based diagnostic and treatment plans. Fulfilling the ethic of care may involve being equipped to empathetically understand and respond to a patient's emotional and psychic reactions to bad news about her health. The manifestations of these dimensions within the caregiver-patient relationship will vary in prominence in different circumstances but always remain distinct from other dimensions and should always be guided by the ethic of care.

Different relationships must interact with each other if the ethic of care is to optimally serve patients. One caregiver, often a physician or nurse practitioner, may need to co-ordinate activities of other caregivers to maintain the focus of meeting all patient needs. Primary caregivers may draw on the specialized caregiver colleagues to more effectively meet certain diagnostic and therapeutic patient needs. Primary care physicians may also interact with nurses, social workers, psychologists and the patient's supporting loved ones with the intention of addressing and meeting diverse patient health care needs under 'an ethical umbrella' of care.

Within a Reformational worldview, professional practices, including medical practices, have *normative* principles, originally grounded in the divine call to human obedience at the beginning of creation. Despite the encroachment of sin, by God's grace such principles have remained in his written Word and through the human conscience. In medicine,

1 James Rusthoven, *Covenantal Biomedical Ethics for Contemporary Medicine*. Eugene, OR: Pickwick Publications, 2014.
2 Henk Jochemsen, "Normative Practices as an Intermediate between Theoretical Ethics and Morality," Philosophia Reformata 71 (2006): 96–112.

normative principles of medical practice can be violated when a caregiver's focus on the ethic of care drifts toward self-interest. Such a change in focus can be seen as a form of reductionism; that is, the direction and content of complex tasks required to maintain focus on patients' multifaceted care needs are reduced to self-serving alternative decisions and actions. For example, companies that produce and market cancer therapies often send representatives to physicians' offices to promote their company's products. This can involve a discussion regarding the purported benefits of a therapy, an invitation to attend a conference promoting the therapy with costs covered by the company, and/or a grant toward the physician's research. Such promotion is focused on convincing the physician caregiver, at least partly through various coercive enticements, to consider buying and using their therapy over those of competitors. This interaction may subvert the caregiver's normal decision-making process whereby treatments are selected solely on the balance of benefits and risks of various therapies characterized in evidence-based publications. In my own practice, as I became increasingly aware of the dangers of such enticements, I would avoid meeting with pharmaceutical company representatives. If they happened to cross my path on their way out, I would thank them for the articles about their products that they invariably left with my administrative assistant, assuring them appreciatively that my training gave me the expertise to interpret such literature as it may help me to make informed recommendations for my patients.

Inappropriate focus on economic gain can also affect relationships between physicians and their supporting institutions. A number of years ago the administration of several effective chemotherapeutic agents had changed so that patients could be treated safely and less expensively in outpatient clinics rather than on a hospital ward as had been the previous practice. While most oncology practices in Canada followed this change, some persisted in treating their patients in hospital. The main incentive appeared to be that physicians were paid more by the province for administering cancer therapies in hospital rather than in the clinic. Yet evidence showed that in-hospital administration did not improve treatment outcomes while in-hospital treatment did increase the risk of contracting antibiotic-resistant infections, required patients to take more time off from work and other activities, and increased the cost to the hospital.

While economic self-interest and gain is not the only type of activity that may distort normative medical practice, and it has decreased in recent years through

improved codes of conduct and education, it remains an ethical stumbling block for physicians. I have found the Reformational worldview to be helpful in guarding against inappropriate economic influence in discussions with colleagues and in teaching sessions with students. This worldview has been helpful in putting forward the essential suppositions regarding what constitutes a normative practice and how their distortion can lead to reduction in the quality of patient care. It can sharpen one's alertness in identifying activity and decisions leading to unethical and self-serving behaviour and adverse consequences. Attention to normative practices is applicable to all relationships whose singular focus on the ethic of care makes up the core meaning of medical practice.

More recently I was called to the field of regulatory medicine as a medical officer and evaluator of new cancer therapies at Health Canada. In the next section I reflect on my regulatory experience in the Canadian health care context. As in the clinical practice setting, I have found a Reformational worldview to be no less helpful in discerning normative from anormative expressions of decision-making in the field of new cancer drug regulation. While the relationships in regulatory medicine do not involve patients directly, evaluation of new cancer drugs for marketing is still focused on the ethic of care. Relationships involve stakeholders such as pharmaceutical companies (known as sponsors in this context), government regulators, expert medical practitioners and patient advocates for patients as the benefactors of effective and safe new therapies. Again, a Reformational worldview can help to understand normative processes and decision-making as well as improve vigilance

against distortions that can lead to unethical thinking and decision-making.

New Drug Regulation

Importance of Clinical Trial Designs, Therapeutic Uncertainty and Ethical Implications

Under legal regulations and guidance policies adhered to by most international regulatory jurisdictions, new therapies for the treatment of cancer are tested in clinical studies to evaluate their efficacy and safety compared to existing standard therapies. The best-designed clinical trials directly compare, in the same time frame, efficacy and safety results from patients receiving a new therapy to those receiving a current standard of care (the control group). These are clinical experiments asking two closely related questions: for a defined group of cancer patients, is a new treatment beneficial as well as safe such that the likelihood of meaningful benefit outweighs the risk of substantive ill effects?

Arguably the most important characteristic that distinguishes the quality of different designs of clinical studies is the ability to produce a result that confidently reflects only the influence of the new drug on patient well-being; that is, in high quality studies, any influence of known and unknown confounding factors is minimal and consequently an erroneous result is very unlikely. Excluding such adverse influences on study results is best assured by random allocation of eligible patients to either current standard therapy or the new therapy. The process of random allocation is like flipping a coin for each enrolled patient: heads and you get the new treatment, tails and you get the current proven standard treatment. For example, if more patients with earlier stages of cancer receive a new drug compared to those receiving standard therapy, this factor may add to an improved result for patients receiving the new drug. This contribution would thus confound a claim that treatment with the new drug alone is responsible for the better result. Most importantly, results of studies influenced by such confounding factors can lead to significant uncertainty for oncologists and their patients as to whether a new drug is truly better than previous standard therapies.

Thus, random allocation of patients to study treatment options is at the core of most ethically robust clinical studies and such studies are generally the main or pivotal studies in new drug applications. They provide the best evidence for considering approvability for marketing in Canada. However, random allocation is ethical only if both physicians and study subjects are genuinely uncertain as to whether the new drug is better for the subject than the existing standard therapies before the study begins.

Unfortunately, in some new drug submission portfolios, no studies include randomization, increasing the uncertainty that the results may truly reflect the effect of the new drug alone. In some such studies, all enrolled patients may be assigned to receive only the new therapy and claims of improved efficacy and/or safety by the sponsor can only be made by comparing the results with previous studies of standard therapy. Such historical comparisons can be fraught with risks of confounding factors involving time and historical circumstances that could cast doubt on any claim of improved efficacy. When no control group is embedded in the study and end points such as tumour shrinkage and the duration of shrinkage are the major end points, there is low confidence in reliably inferring true

improvement in survival attributable to the new drug alone. That is, in this design, it cannot be concluded that the overall survival of patients, the most meaningful outcome, will be improved due to administering the new drug. As a result, sponsor claims of better efficacy, particularly better survival, carry a high risk of being false.

The regulatory and ethical responsibilities of the sponsor of a new drug to carry out studies designed to give an acceptable degree of certainty in the results are often in direct conflict with the business interests of minimizing costs while maximizing profits (this will be discussed more below). The ethical bar of 'acceptable degree of certainty' is set by the regulator, driven by the primary function of authorizing the best treatments that satisfy the ethic of care for needy patients.

However, that bar is regularly challenged by sponsors, claiming less costly studies with no randomization or even with no control group can be conducted more quickly while, in the sponsor's judgment, providing a sufficient level of evidence. For different reasons, other stakeholders such as patient advocates may also argue against randomized trials that require more time to mature. However, their primary motivation is a faster time to completion and hopefully faster approval for their clients.

Consequently, the relationship between sponsors and regulators can be tense due to differing claims regarding the degree to which results show *clinically meaningful* improvement in patient care attributable to a new drug alone. For example, a sponsor may provide suggestive evidence that their new drug alone shows meaningful tumour shrinkage *and* is sufficient to predict a longer life for the treated patients. Yet, well-implemented published studies may not support such a predictive claim, raising ethical questions of appropriate interpretation. Sponsors may present testimonies from influential physicians and/or affected patients in an emotional appeal to override the published evidence. In such cases, the decision-making process can be complex and methods to sway reviewers away from judgments based on sound evidence are ethically dubious at best. Additional ethical questions relate to the acceptable level of risks of serious side effects, including death. In my experience, mentoring colleagues through a Reformational perspective improves their ability to identify ethical concerns about suboptimal clinical trial designs and misinterpretations of results affected by inappropriate influence of other stakeholders in the regulatory review process.

Motives that drive strategies for new drug development

Sponsors

As mentioned earlier, sponsors establish relationships and make decisions for their businesses guided strongly by the economic dimension or aspect. This directing dimension guides other dimensions toward the goal of financial gain as a return on investment for shareholders and more capital for corporate growth. Consequently, as a business, the economic dimension heavily influences all decisions in new drug development planning. Improving patient care is important but is often subsumed by economic considerations. Sponsors must balance the regulations that govern what clinical information is required for marketing approval against the cost of conducting the clinical studies that generate such information. Consequently, there is a primary economic motive to conduct less costly studies over the shortest period of time possible to beat competitors to market while still convincing regulatory reviewers that their drug is meaningfully better and at least no less safe than the current standard therapy. It is a calculated business risk, since conducting less expensive, non-randomized trials can introduce sufficient uncertainty about efficacy and/or safety that regulators may not give approval. It is also a calculated ethical risk; their primary economic focus often clashes with the primary regulatory focus of approving better therapies to contribute to the ethics of care. Regulators may feel pressure to accept results and approve drugs based on lesser degrees of certainty from not only sponsors but from other stakeholders such as practising physicians, patient advocates and patients themselves.

Patient Advocacy Groups

Patient advocacy groups for cancer patients also focus on the ethical dimension of patient care but this is expressed through advocating for better care and services for patients with specific types of cancer, even if at the expense of those outside of their advocacy responsibilities. This could involve advocating for faster development of better treatments and better insurance coverage for patients with specific cancers. Their lobbying may pressure regulators to "cut corners" by accepting from sponsors smaller studies with less control over confounding factors and thus more uncertainty over efficacy, for the sake of faster approval. Such zealousness for their client-patients can lead to the pursuit of fiscal and other limited health care resources at the expense of patients with other types of cancer. The ethics of lobbying for such patients are complex, involving health care providers, their supporting institutions whose resources support the specialized care of such patients, and provincial insurers of health care. Viewed by many patients and their physicians and nurses, this activity can be ethically meritorious as a voice for those who are unable to speak effectively for their particular health care needs. However, such activity can also be a conduit for assisting unethical health product promotion by sponsors who may preferentially pay physicians to participate in various promotional forums. A more soundly ethical and stewardly approach would involve the provision of equal opportunity for various advocacy groups to formally make their case before provincial health ministries for improving resources to meet their clients' needs. The provincial ministries might then more justly make the difficult decisions of distributing limited resources within cancer care sectors of the health care system within their jurisdictions.

Cost-Effectiveness Analyses and Health Insurance Providers

Like sponsors, health insurance providers assess the cost-effectiveness of new drugs. In Canada, Health Canada assesses the benefits and risks of new cancer therapies but explicitly excludes any consideration of cost in the decision. Following marketing authorization, an independent, not-for-profit health technology assessment (HTA) usually determines the cost-effectiveness of the new therapy. The HTA then advises each provincial Ministry of Health (MOH) whether or not they conclude that a new cancer therapy is sufficiently cost-effective to warrant funding. Each MOH ultimately decides whether such funding will be granted based on the realities of their health care budgets. Like medical practice and regulatory medicine, each Ministry of Health is also guided primarily by an ethic of care for its citizens. Like other stakeholders with relationships in medicine, it must keep this ethic of care in focus and avoid economic and self-serving interests of specific groups and stakeholders to ensure a just distribution of limited funding across populations of patients with a wide variety of diseases.

Conclusions

Thus, the directing ethical dimension or aspect as an ethic of care exists in different domains of medical care. Its expression in these domains can provide very different ethical challenges in meeting patient needs competently and equitably at the individual patient, clinic practices and provincial insurer levels. A biblical Reformational worldview can increase awareness of distortions to medical care such as temptations for economic gain or personal self-interest that may interfere with the focus on patient care needs. All stakeholders in the medical care enterprise should work together to avoid influences that would detract from the focus on the ethic of care.

Much development of a Reformational worldview has been at the theoretical level, yet in recent years it has been applied directly to an increasing number of disciplines and vocations. I have found that the Reformational worldview can give helpful guidance for stakeholders in health care to maintain a primary focus on patient needs while balancing multiple relational dimensions that characterize relationships within different fields of medicine.