MEDICAL EDUCATION AND FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS WITH THE PHARMACEUTICAL INDUSTRY IN CANADA: AN ANALYSIS OF FOUR AREAS OF MEDICAL EDUCATION

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ABSTRACT

Financial conflict of interest (FCOI) relationships in medicine have been found to expose medical education in medical schools, medical journals, and continuing medical education (CME) hosted by professional medical associations (PMAs) to vulnerability to corporate bias. Institutional policy analysis concerning FCOI relationships and industry involvement in medical education in Canada is limited. Therefore, informed by neoliberal corporate bias theory and Mertonian norms of science, this dissertation contributes analyses of conflict of interest policies, disclosures, and opportunities for drug company involvement in the production and dissemination of medical knowledge. In a publication-based dissertation format, the first manuscript provides an evaluation of conflict of interest policies at the 17 medical schools in Canada. The second manuscript provides an analysis of the culture of corporate science, informed by neoliberal ideology, through an examination of the extensive and pervasive roles of the drug promotion industry in clinical trial research, interpretation, writing, and publishing in medical journals. The third manuscript offers an evaluation of policies concerning FCOI relationships and industry involvement in CME development and programming adopted by 60 professional medical associations in Canada. The fourth and final manuscript comprises an quantitative analysis of FCOI relationship disclosures in Canadian clinical practice guidelines. In general, these evaluative efforts found that the policy environment concerning industry involvement in various types of medical education in Canada is permissive and FCOI relationships are common among guideline authors. Positioned within the context of neoliberal corporate bias theory and Mertonian norms of science, these findings of general policy

permissiveness indicate an alignment of goals between the pharmaceutical industry and medical education institutions. The necessity for increased transparency in terms of industry's roles in not only conducting, analyzing, interpreting, and publishing pharmaceutical research, but also data sharing is supported by existing literature on financial conflict of interest relationships with the pharmaceutical industry. Furthermore, the strengthening and enforcement of policies on industry involvement and FCOI relationships in these areas of medical education would help to ensure that medical education in the public's interest is achieved.

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LIST OF ABBREVIATIONS

AAMC – American Association of Medical Colleges
ABIM-IMAP – American Board of Internal Medicine-Institute on Medicine as a Profession
ACC – American College of Cardiology
ACCME – Accreditation Council of Continuing Medical Education
ACRO – Association of Clinical Research Organizations
ADRs – Adverse drug reactions
ADVANTAGE – Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness
AEI – American Enterprise Institute
AFMC – Association of Faculties of Medicine of Canada
AHA – American Heart Association
AHC(s) – Academic health centre(s)
AMCs – Academic medical centres
AMSA – American Medical Students Association
AMWA – American Medical Writers Association
AWMF – Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of Scientific Medical Societies in Germany)
BBC – British Broadcasting Corporation
BMJ – British Medical Journal
CADTH – Canadian Agency for Drugs and Technologies in Health
CBC – Canadian Broadcasting Corporation
CCI – Commercially confidential information
CDER – Center for Drug Evaluation and Research
CFPC – College of Family Physicians of Canada
CJC – Canadian Judicial Council
CMA – Canadian Medical Association
CME – Continuing medical education
COI – Conflict of interest
COPE – Committee on Publication Ethics
CPD – Continuing professional development
CPGs – Clinical practice guidelines
CPS – Compendium of Pharmaceuticals and Specialties
CPSO – College of Physicians and Surgeons of Ontario
CRFs – Case report forms
CRO(s) – Contract research organization(s)
CSCJA – Canadian Superior Courts Judges Association
CSRs – Clinical study reports
DDMAC – Division of Drug Marketing Advertisements and Communications
DIDA – Drug Industry Document Archive
DSM – Diagnostic and Statistical Manual of Mental Disorders
DTCA – Direct to consumer advertising
DTPA – Direct to physician advertising
EBM – Evidence-based medicine
EFPIA – European Federation of Pharmaceutical Industries and Associations

EMA – European Medicines Agency
EMWA – European Medical Writers Association
ENHANCE – Ezetimibe Plus Simvastatin Versus Simvastatin Alone on Atherosclerosis in the Carotid Artery
FCOI – Financial conflict of interest
FDA – Food and Drug Administration
GDG – Guideline development group
GSK – GlaxoSmithKline
HAI – Health Action International
HMD – Health and Medicine Division
ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE – International Committee of Medical Journal Editors
ICRC – Inquiries, Complaints and Reports Committee
IFPMA – International Federation of Pharmaceutical Manufacturers and Associations
IOM – Institute of Medicine
IP – Intellectual property
IPPA – International Publication Planning Association
IRB(s) – Institutional review board(s)
ISMPP – International Society for Medical Publication Professionals
JAMA – Journal of the American Medical Association
KOL(s) – Key opinion leader(s)
MBM – Marketing-based medicine
MCC – Medical communications company
MCCs – Medical communications companies
MEC – Medical education company
MECCs – Medical education communication companies
MESS(s) – Medical education service supplier(s)
MWO(s) – Medical writing organization(s)
NASs – New active substances
NDAs – New drug approvals
NEJM – New England Journal of Medicine
NGC – National Guideline Clearinghouse
NHS – National Health Service
NIH – National Institutes of Health
NMEs – New molecular entities
NOSM – Northern Ontario School of Medicine
PHI – Personal health information
PhRMA – Pharmaceutical Research Manufacturers of America
PILs – Patient information leaflets
PLoS Medicine – Public Library of Science Medicine
PMAs – Professional medical associations
PPSA – Physician Payment Sunshine Act
PR – Public relations
PREDICTIVE – Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation

PSRIs – Public sector research institutions
R&D – Research and development
RCPSC – Royal College of Physicians and Surgeons of Canada
RCTs – Randomized controlled trials
REBs – Research ethics boards
SABs – Scientific advisory boards
SAEs – Serious adverse events
SMO(s) – Site management organization(s)
SPC – Summary of product characteristics
SSRI – Selective serotonin reuptake inhibitor
STEPS – Study of Neurontin: Titrate to Effect, Profile of Safety
TTID – Truth Tobacco Industry Document
UCSF – University of California San Francisco
UK – United Kingdom
US – United States
WHO – World Health Organization

CHAPTER 1

INTRODUCTION

FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS WITH THE PHARMACEUTICAL INDUSTRY IN THE FIELD OF MEDICINE

1.1 BACKGROUND AND CONTEXT

In 1998, the British Broadcasting Corporation (BBC) cancelled a £360,000 television series that received good reviews because of a "potential conflict of interest" where the producer of the show owned commercial property that was featured in the episodes (Smith, 1998). In 2015, two news television personalities were sanctioned for engaging in undisclosed financial conflict of interest (FCOI) relationships: One anchor at the Canadian Broadcasting Corporation (CBC) was fired for creating FCOI relationships by brokering the sale of and receiving commissions on paintings for people that he had dealt with in his role as a high-profile host of a popular CBC television show. The other, at Global Television, was suspended indefinitely for his role as a part-owner of a public relations firm, some of whose clients were featured on the anchor's television show (Donovan, 2015; The Canadian Press, 2015). Following the CBC's firing of its anchor, it instituted a ban on participating in paid appearances that were external to the CBC for all of its on-air journalists. The CBC issued a memo which stated that "[g]iven that paid

appearances can create an adverse impact on the Corporation, CBC/Radio-Canada will no longer approve paid appearances by its on-air journalistic employees" and that "a changing environment in which the public expects more transparency from institutions and the media is making the practice of paid outside activities for our journalists less acceptable to audiences" (Houpt, 2015). At least five other well-known CBC news anchors have been similarly criticized for potential conflict of interest (COI) relationships by receiving payments from organizations external to the CBC for speaking, travel expenses to speaking engagements, moderating seminars, and making appearances (Houpt, 2015).

Professions including law, accounting, engineering, and architecture have recognized the importance of regulating COI relationships through policies and ethical codes to promote objectivity and maintain public trust (Institute of Medicine [IOM], 2009). For example, in Canada, the United States, and the United Kingdom, judges are subject to recusing themselves from hearing cases when there is a reasonable apprehension of bias. Regarding Canadian law specifically, the Canadian Judicial Council (CJC) advises that

> Judges should disqualify themselves in any case in which they believe that a reasonable, fair minded and informed person would have reasoned suspicion of conflict between a judge's personal interest (or that of a judge's immediate family or close friends or associations) and a judge's duty (Canadian Judicial Council, 2004).

Furthermore, in Canadian law, recusal is considered within the context of impartiality which is concerned with both perception and, more fundamentally, the actual absence of bias and prejudgement. According to the CJC, the test to determine impartiality in Canada is whether:

> …'an informed person, viewing the matter realistically and practically – and having thought the matter through –' would apprehend a lack of impartiality in the decision maker. Whether there is a reasonable apprehension of bias is to be assessed from

> the point of view of a reasonable, fair minded and informed person … 'True impartiality does not require that the judge have no sympathies or opinion; it requires that the judge nevertheless be free to entertain and act upon different points of view with an open mind' [and that the] judge's fundamental obligation is to strive to be and to appear as impartial as possible. This is not a council of perfection. Rather it underlines the fundamental nature of the obligation of impartiality which also extends to minimizing any reasonable apprehension of bias (Canadian Judicial Council, 2004).

Moreover, according to the Canadian Superior Courts Judges Association (CSCJA), judges play many roles including interpreting the law, analyzing and assessing the presented evidence, and controlling the manner in which hearings and trials unfold in their courtrooms (Canadian Superior Courts Judges Association [CSCJA], 2006). Applying the CSCJA's (2006) interpretation of the roles of judges, judges and physicians have similar roles in their respective professions. Like judges, it is part of a physician's professional role to interpret, analyze, and assess medical research and evidence concerning various medical and non-medical, prescription and non-prescription treatment options for their patients. Physicians, as with judges, are often in the position of deciding between two or more opposing views and must then "try the facts" to decide whether evidence presented to them is credible and if those who are providing the evidence are telling the truth.

Just as judges are supposed to operate above the fray or dispute, physicians ultimately make their own independent and impartial assessments of the facts. Therefore, physicians and medical researchers, which hereafter will be collectively referred to as physicians unless referring to non-physician researchers or medical students, ought to be held to similarly stringent conflict of interest standards because they hold authoritative positions with which they can broadly influence treatment practices and research questions in both the medical practice and medical education realms. The effects of these

relationships can knowingly or unknowingly affect physicians' teaching at medical schools, publishing articles and reviews in respected peer-reviewed medical journals, membership on committees that develop clinical practice guidelines (CPGs) and speaking at and organizing continuing medical education (CME) programs hosted by professional medical associations (PMAs).

Compared to other professions, including law, accounting, engineering, and architecture, regulating conflict of interest relationships in medicine is relatively new (Rodwin, 1993). Similarly, the term "conflict of interest" is relatively new, with its first use in a court case in 1949 and its first appearance in an English dictionary in 1971 (IOM, 2009). Prior to the 1970s, terms similar to "conflict of interest" such as "adverse interest", "conflicting interest", "bias", and "prejudice" were used (IOM, 2009). Detailed provisions on COI relationships have been adopted within research ethics guidelines and regulations by various medical specialty organizations and medical research institutions. Many of these provisions exist within the bylaws and policies adopted by medical colleges and specialty societies (IOM, 2009). However, despite the adoption of these policies, regulation of COI relationships in medicine remains piecemeal, fragmented, and non-uniform. The regulation of COI relationships in medicine also serves as a model for the regulation of COI relationships in other regulated health care professions including osteopathy, dentistry, pharmacy, nursing, chiropractic, and others (IOM, 2009).

Financial relationships between medical professionals and the pharmaceutical industry have come to undermine the confidence and trust that the public affords to physicians and medical researchers, as well as the integrity of medical professionals' opinions and publishing interests (Cho, Shohara, Schissel, & Rennie, 2000; DeAngelis,

2000; Ehringhaus et al., 2008; Tattersall, Dimoska, & Gan, 2009). Medical education and research institutions and professional organizations should adopt and enforce established policies to address FCOI relationships, or where there are none create them, in the interest of the public. These policies should serve as genuine efforts to ensure that the medical professionals at those institutions and organizations make decisions based on their primary interests, not secondary interests, as dictated by their professions' standards (IOM, 2009). FCOI relationships can compromise professional judgement through bias as well as other practices that violate standards of professional conduct and policies should be developed to help medical professionals safeguard against the influence of secondary interests. Studies which evaluated behaviours in the medical field before and after FCOI policy implementation have found that institutional and organizational policies can provide the most significant and meaningful protection against the possible consequences of professionals' engagement in financial conflict of interest relationships (Grande, Frosch, Perkins, & Kahn, 2009; IOM, 2009; King, Essick, Bearman, Cole, & Ross, 2013; Langer et al., 2012). It is these relationships that tend to have excessive influence on professionals' decisions about research conduct, teaching, treating patients, and the development of CPGs (IOM, 2009).

The regulation of FCOI relationships between medical professionals and the pharmaceutical industry through the adoption of formal institutional policies is the focus of this dissertation. According to the IOM (2009), policies are most effective when they are preventive and corrective, rather than punitive. Policies can be effective in two important ways. First, policies can uphold the integrity of professional judgement and, second, preserve public trust and confidence in those judgements. These two objectives

should be the fundamental and primary goals of any meaningful conflict of interest policy. Importantly, these policies should not assume that any individual physician or medical researcher will inevitably allow financial interests to influence his or her judgements. Further, these policies should not imply that individual physicians or medical researchers are unethical people. Rather, the basis of FCOI policies should be the assumption that under certain conditions, there are risks that decisions may be unduly influenced by secondary interests (IOM, 2009).

Physicians and medical researchers may sometimes be offended by assertions that they have engaged in FCOI relationships with drug companies and believe that these sentiments challenge their ethical integrity. Because of these sensitivities, the IOM states that some institutions have replaced the term "conflict of interest" with phrases including "relationships with industry" or "financial relationships" to describe relationships that are potentially conflicted or may be judged to constitute COI relationships. The IOM (2009) argues that using this filtered and less direct language obscures the serious risks that COI relationships pose. Furthermore, the IOM reasons that this language is unnecessary if it is recognized that the judgement that an individual has a COI is a reflection of the situation and not of the professional who is in the situation (IOM, 2009).

Further to this point, professionals accused of having a COI relationship often respond that they would never personally allow financial interests to influence their professional judgement but it is more likely that their colleagues would be influenced (IOM, 2009; Lieb & Brandtonies, 2010; Orlowski & Wateska, 1992). This position is not a justifiable objection to the development and adoption of meaningful conflict of interest policies because a conflict of interest, as previously defined, is a situation or set of

conditions involving risk. Therefore, conflict of interest policies should not be directed toward specific motivations for decisions that individual professionals make or imply that these professionals are improperly motivated. Should conflict of interest policies be driven by these factors, professionals could respond that it is unfair to generalize in this manner and that their actual decisions and distinguished reputations would prove otherwise. However, good conflict of interest policies avoid having to investigate on a case by case basis (IOM, 2009).

The IOM (2009) committee argues that conflict of interest policies need not focus on the motivations for individuals' decisions for two central reasons: first, they argue that reliably determining or inferring motive in this context is usually impossible and this sort of investigation would be not only unnecessarily intrusive, but also highly time-consuming. Medical research, education, and patient care decisions are typically the result of many smaller judgements and decisions that are impractical and virtually impossible to review and even if they were reviewed, it is unlikely that this effort would generate a clear illustration of the individual's underlying motives. For the same reasons, readers of medical journal articles, medical students, patients, and conflict of interest committees are unable to judge whether secondary, financial interests motivated a certain decision. Furthermore, those who are affected by the results of research, the content of lectures, or drug prescriptions are typically not in a position to be able to judge the legitimacy of the professional's decisions. Even when people can make these judgements, this is usually possible only after the damage has occurred. Investigating individuals after the fact, in order to avoid having well-rounded preventative conflict of interest policies in the first

place also has the potential to violate the rights and privacy of individuals who might be involved in the decision-making process (IOM, 2009).

This dissertation supports the IOM's position on developing well-rounded, preventative COI policies with provisions on enforcement and dealing with violations when they occur. Research on both COI relationships and related policies can provide a stronger evidence base for policy design, development, and implementation and has the potential to provide institutions and organizations with the information necessary to develop the necessary policies (IOM, 2009). This dissertation argues that the principle goal of conflict of interest policies should be to protect and preserve the integrity of medical research, professional judgement, and public trust. In contrast, the goal of conflict of interest policies should not be to mitigate bias or mistrust of medical research or professional judgement after it occurs, although inclusion of prescribed processes to deal with these situations, should they occur, is also important (IOM, 2009).

There are significant gaps in the conflict of interest literature in Canada, particularly in terms of policy evaluation and assessments of disclosures. Therefore, this dissertation comprises four manuscripts which evaluate the Canadian context of conflict of interest policies and disclosures in different medical fora in which medical education occurs. In this dissertation, the term "medical education" is used broadly to refer to the various ways in which clinical research results are disseminated to physicians, medical researchers, and medical students. Medical education, as it is used in this context, refers to a wide variety of medical materials and methods of distribution that are used to teach and inform physicians, medical researchers, and medical students about clinical knowledge and advancements required for medical practice and research. For example, medical students

receive the foundations of their medical knowledge in medical schools from physician or medical research faculty. Physicians receive updates and new medical treatment standards from CPGs.

Physicians are also required to engage in accredited CME or continuing professional development (CPD). In 2011, the government of Ontario made CPD mandatory for physicians in Ontario (College of Physicians and Surgeons of Ontario [CPSO], 2012). The consequences for failing to engage in CPD in Ontario are an assessment of the physician's practice, or an investigation into professional misconduct by the Inquiries, Complaints and Reports Committee (ICRC) of the College of Physicians and Surgeons of Ontario (CPSO) (CPSO, 2012). Physicians typically rely on their respective medical associations to provide opportunities for accredited CME programs. Finally, medical students, physicians, and especially medical researchers regularly consult peer-reviewed medical journals for published articles on clinical trials, the safety and efficacy of new drugs, and review articles summarizing the results of these studies.

This broad conceptualization of medical education is both necessary and important in order to comprehensively capture the spectrum of methods by which medical knowledge is disseminated and sought out by medical professionals and students. Ultimately, inclusion of the many ways that medical schools, medical societies, medical journals, and the pharmaceutical industry consider providing medical education is crucial to a comprehensive assessment of the various ways in which FCOI relationships are handled. Although this is not an exhaustive list, these categories of medical education are the focus of this dissertation.

The four studies that comprise the central component of this dissertation are situated within the context that biomedical research and knowledge is increasingly a product of privatized and commercialized science and this has occurred partially through the development of FCOI relationships between drug companies and physicians. These ties serve as vectors by which science for commercial consumption is developed and disseminated and, therefore, must be regulated. Institutional policies are at the core of the efforts to regulate FCOI relationships. In order to determine whether FCOI relationships are effectively addressed, considered, and regulated, these policies must undergo analysis.

1.2 OUTLINE OF THE DISSERTATION

The literature review (Chapter 2) follows this introductory chapter. The literature review provides additional context for the practical placement of this dissertation within the existing literature base on the relationships between physicians and the pharmaceutical industry. The literature review addresses issues such as defining conflict of interest relationships in medicine, the need to and rationale for focusing on financial relationships in medicine, counterarguments to the perspective that FCOI in medicine should be regulated, industry involvement in medical research and research integrity, and disclosures of FCOI relationships in medical education.

The theoretical chapter (Chapter 3) follows the literature review. This chapter considers that, although science has never been free from outside influence, the interactions between public science and private profit have dramatically shifted since the 1980s. This shift is, in large part, due to the widespread global drive toward neoliberalism.

Neoliberalism advocates for an ideal economy as a “marketplace of ideas”, where its fundamental role is to process and convey knowledge or information rather than to exchange material things. Neoliberal ideology assumes that it is impossible for human beings to create, encompass, or predict such an abstract marketplace that is able to simultaneously convey existing ideas and mobilize further innovation. Rather, this outcome is achieved by redefining the organization of knowledge using market-based solutions. These solutions have been made possible through the development and adoption of both national and international neoliberal-oriented policies that encourage and support private investment in science and university-industry partnerships.

The uniqueness of neoliberalism is that it alters the very nature and existence of not only the market, but also society. Through the adoption of neoliberal policies, the methods, organization, and content of science ultimately changes. The movement toward neoliberalism, therefore, has had, and continues to have, profound and lasting implications on the organization, practice, and integrity of science (Krimsky, 2004; Lave, Mirowski, & Randalls, 2010). For example, a significant consequence, which will be interrogated in Chapter 5, is the commercialization of research through FCOI relationships with researchers as well as sponsors’ involvement and potential for control over all aspects of the research process. This control may range from the conceptualization of studies, to data collection and analysis, to writing and preparation of manuscripts, to correspondence with target journals regarding manuscript submission and revisions, to publishing through a process called ghost management. This process has also resulted in the dissolution and disappearance of the scientific author, with the proliferation of the medical ghostwriting

and ghost management industries, which epitomize the commodification of medical research (Mirowski, 2001; Sismondo, 2007, 2009).

This dissertation uses Philip Mirowski's work on the recent transformations in science as a consequence of neoliberal policies (Lave et al., 2010; Mirowski & Van Horne, 2005; Mirowski, 2001, 2011) to investigate medical professionals' participation in FCOI relationships with the pharmaceutical industry in each of the four manuscripts within this dissertation and to provide a snapshot of the current medical research and conflict of interest environments. This dissertation also applies work by Sergio Sismondo on the ways in which the commercialization and commodification of medical research has resulted in the growth of the medical ghostwriting and ghost management industries (Sismondo, 2003, 2007, 2011, 2012), both of which embody the very nature of Mirowski's notion of the neoliberal "marketplace of ideas" in the changing landscape of scientific research (Lave et al., 2010; Mirowski & Van Horne, 2005).

It is within this theoretical context that this dissertation positions the relevance and importance of FCOI relationships with industry. These formed relationships between physicians and the pharmaceutical industry are the vectors by which the nature of medical research has been, and continues to be, transformed. Similarly, these relationships support and contribute to the shifts in the ways that medical research is conceptualized, conducted, and organized. FCOI relationships with the pharmaceutical industry have led to consequences for physicians' research interests as they might be limited to those which are commercializable rather than disinterested research for the purpose of scientific inquiry. These consequences extend to the delay in publishing research results, suppression of

negative results, and sponsors' control over manuscript contents by requiring researchers to allow prepublication review of studies.

Research on the consequences of FCOI relationships in medical education and research, coupled with the above theoretical perspective, have led to the four manuscripts (Chapters 4-7) that comprise the central pillars of this dissertation. Finally, this dissertation closes with the conclusion (Chapter 8), which provides both general and specific conclusions based on the findings of the four manuscripts as well as recommendations for further research and action.

1.3 THE FOUR MANUSCRIPTS

1.3.1 Chapter 4 – Too Few, Too Weak: Conflict of Interest Policies at Canadian Medical Schools

Attitudes toward conflict of interest relationships with the pharmaceutical industry begin forming in medical school, when medical students are exposed to and taught by faculty, who may be academic physicians or medical researchers, who may have financial ties with drug companies. Medical students are also exposed to considerable contact with pharmaceutical marketing, which impacts future clinical decision making (Austad, Avorn, & Kesselheim, 2011). Industry involvement and influence in medical education manifests in multiple forms and at many levels, which may not always be easily identifiable. For instance, industry involvement and influence can occur when one or more drug companies sponsor education events, education materials, scholarships or awards, and clinics, laboratories, classrooms, and buildings in which medical students are trained. The

pharmaceutical industry may also have considerable influence over medical faculty, for example, when they receive money from industry for research, consulting, travel to medical meetings and CME activities, as well as participating in speakers' bureaus, functioning as clinical trial investigators or recruiting patients, or for publishing industry sponsored research and review articles.

Drug companies recognize that medical education is a fertile forum in which marketing strategies and messages can be masked as education. Medical students and academic physicians, who have graduated from medical school, have expressed and documented their concerns that the exposure of medical students to covert and overt industry influence has promoted a shift in prescribing and overuse of specific products for uses that are inconsistent with current best evidence practices. Exposure to industry influence as early as undergraduate medical education shapes physicians' attitudes from the beginnings of their careers and plays a lasting role in shaping their clinical perspectives and behaviours (King et al., 2013; McCormick, Tomlinson, Brill-Edwards, & Detsky, 2001; Persaud, 2013; Ubelacker, 2010). The early and continued exposure to industry influence leads to the presence of industry becoming omnipresent and normative.

Physicians trained in residency programs with policies that limit contact with industry representatives have been shown to be more critical of information that they receive and they are less likely to prescribe costly, highly marketed, and risky medications when there are other safer and more cost-effective medications approved for use (Epstein, Busch, Busch, Asch, & Barry, 2013; King et al., 2013; McCormick et al., 2001). In spite of these findings, Paul Hébert and colleagues found that medical students in Canada are not protected from industry influence because Canadian medical schools' conflict of

interest policies fail to effectively regulate relationships with industry (Hébert, MacDonald, Flegel, & Stanbrook, 2010). Ghislaine Mathieu and colleagues (2012) also found COI policies at Canadian universities to be generally weak in regulating faculty-industry relationships, receipt of samples, seeing sales representatives, on-site and off-site training, and inclusion of education on COI relationships within the curriculum (Mathieu et al., 2012). This study's limitations included that the authors evaluated university-wide policies only, rather than including medical school-specific policies. Additionally, Northern Ontario School of Medicine (NOSM) was excluded from the study. The authors also did not contact the deans of the medical schools to ensure the completeness of their list of policies and relied solely on those found through a web search. Finally, the policies were evaluated by a single coder. The other study that evaluated COI policies at Canadian universities also analyzed only university-wide policies and included only 13 of the universities in Canada (Williams-Jones & MacDonald, 2008).

To address these limitations, Drs. Joel Lexchin, Barbara Mintzes, Annemarie Jutel, Kelly Holloway, and I conducted a comprehensive evaluation of COI policies at all 17 Canadian medical schools. In our policy evaluation, we scored for stringency of conflict of interest policies in 12 categories: gifts and meals, consulting relationships, industry funded speaking relationships and speakers' bureaus, honoraria, ghostwriting, disclosure, industry sales representatives, on-site education activities, compensation for travel or attendance at off-site lectures and meetings, industry support for scholarships and funds for trainees, medical school curriculum, and samples. We also included two measures which evaluated whether the schools enforced these policies. The "Enforcement A" measure asked whether there was a clearly identified party responsible for oversight to ensure compliance and

"Enforcement B" asked whether there were clear sanctions for noncompliance with the policies (Shnier, Lexchin, Mintzes, Jutel, & Holloway, 2013).

1.3.2 Chapter 5 – Honest Authorship: A Glossary and Assessment Tool to Help Predict Vulnerability to Corporate Bias in Manuscripts Submitted to Medical Journals

Medical journals are an important vehicle by which medical information is disseminated to physicians. Over the past decade, editors of prestigious high impact medical journals have commented that medical journals have devolved into "marketing arms" of pharmaceutical companies which are, themselves, marketing machines (Angell, 2004; Smith, 2005). Traditionally, scientific authors collect, analyze, and have access to raw data from which scientific, academic articles are generated (Healy & Cattell, 2003). However, drug companies regularly use scientific literature that is published in peer-reviewed medical journals as marketing mechanisms to promote their products.

The concealment of industry bias in publishing peer-reviewed articles in medical journals is important because these articles are considered to be the most widely accepted and trusted impartial forms of presenting clinical evidence. Unlike pharmaceutical ads in medical journals, clinical trials and review articles published in medical journals possess the acceptance and approval of the journal and may be distributed globally. A clinical trial published in a medical journal may also garner global media coverage, especially if these publications are simultaneously supported and promoted by press releases from the journal and costly public relationships firms hired by the drug company that sponsored the published study. Pharmaceutical companies will sometimes spend over a million dollars

on reprints of a favourable clinical trial to distribute to doctors because these favourable studies are worth thousands of pages in advertising. Similarly, a published study that contains a subtle endorsement for a medication, but does not mention the pharmaceutical company that paid for the writing of the paper, carries more weight with clinicians and patients, especially if the authors include prominent physicians and university professors (Leo, Lacasse, & Cimino, 2011; Smith, 2005).

Modern-day marketing techniques conceal industry's bias by obscuring its role in and control over the scientific process. Works by Mirowski, Robert Van Horne, and Sismondo inform the perspective that the peer-review process is no longer able to serve as a safeguard against publishing clinical and related scientific studies that promote industry's commercial objectives at the expense of public health, data transparency, and true critical analysis of the best available evidence-based medicine (Mirowski & Van Horne, 2005; Mirowski, 2001; Sismondo, 2003, 2011). The scientific process, as well as the political, social, and financial structures in which medical research is conducted has been re-engineered alongside larger political and economic trends toward the privatization of science. Chapter 5 discusses the presence and development of specific indicators that clearly illustrate that the trend toward the production of science for commercial interest has occurred. Because medical journals play an important and authoritative gatekeeping role in disseminating important medical research and knowledge, they must develop mechanisms by which they can safeguard against publishing industry marketing that is masked as scientific, disinterested research.

The published literature on these marketing strategies has documented the shift in the use of scientific and medical research from its traditional role to a newer

commercialized role. With this shift, the roles of medical journals have similarly shifted. Because peer-reviewed medical journals are assumed to publish the highest quality scientific research, which forms the basis for subsequent research and treatment decisions, these journals have a responsibility to the public, researchers, physicians, and patients to ensure that they are publishing the highest quality, most disinterested, and reliable scientific results and interpretations. The privatization and commercialization of the medical research process has resulted in a shift in the way that scientific research is conducted and published. Therefore, medical journals have a responsibility to adapt their peer-review approval and rejection processes as well as their considerations of what constitutes reliable and transparent scientific research to this shift toward commercialized science.

Review of the literature about the undue influence that commercial industry has on the medical research and publication processes identifies three thematic categories in which traditional conceptualizations of the scientific process have been reconceptualised to meet business goals. Medical journals need to be aware of these new conceptions and develop and adopt relevant policies to address them. The four thematic categories that are identified within this manuscript are: (i) financial conflict of interest disclosure, (ii) roles of researchers and authors in the research and publishing processes, (iii) data transparency and the origin of the data and published manuscripts, and (iv) enforcement and sanctions.

Through a literature review, this study has compiled a unique and original glossary of 50 key terms, each of which are classified under one of the four thematic categories, pinpointing where the traditional meanings have been taken advantage of in the interest of commercial success. These terms and their new meanings in medical publishing are

accompanied by an original assessment tool that is informed by the glossary. The assessment tool can be used by researchers and staff at medical journals to predict whether manuscripts submitted to their journals may be vulnerable to corporate bias. Furthermore, medical journals can use this glossary to continue to understand the ways in which the scientific process has been redefined by industry so that they can then ensure that they are publishing research that can be trusted to be accurate and in the best interests of science and the public, rather than the bottom line.

1.3.3 Chapter 6 – Continuing Medical Education and Pharmaceutical Industry Involvement: An Evaluation of Policies Adopted by 60 Canadian Professional Medical Associations

Professional medical associations (PMAs) play an essential role in defining, promoting, and advancing health care standards. Medical associations unite physicians by specialty and subspecialty and play a pivotal role in providing and endorsing medical education. Medical associations also play a highly influential role in defining the specialty's ethical norms, standards, and issue codes of conduct to guide the behaviour of their physician members (Rothman et al., 2009). PMAs are considered to be single interest societies for physicians and provide them with clinical resources, including knowledge dissemination and learning opportunities. PMAs accomplish these goals, while pursuing public agendas and advocating for the interests of not only their members and themselves, but also patients; however, these intentions may be undermined because medical societies receive extensive funding from drug companies (Bernat, Goldstein, & Ringel, 1998; Kassirer, 2007; Relman, 2007; Rothman et al., 2009). The roles of medical societies in

legitimizing medical knowledge and shaping medical discourse by choosing which knowledge to disseminate are important goals to consider alongside their financial relationships and interests. The regulation of these interests through the enforcement of strong policies is of primary importance to shaping the attitudes of both practicing physicians and medical students toward relationships with industry more generally.

The literature base concerning the ethics and conduct of PMAs figures prominently in the discussion of medical education, but the literature pertaining to the regulation of FCOI relationships by these societies is young (Brody, 2010; Cosgrove, Bursztajn, & Krimsky, 2009; Kassirer, 2007). Moreover, there are currently no published papers that explicitly evaluate the policies that have been adopted by medical societies to regulate FCOI relationships between PMAs, their members, and industry. Similarly, there are no published studies, in Canada or elsewhere, that evaluate medical societies' policies specific to financial relationships with industry in the context of providing accredited CME. Therefore, this study will address this gap in the literature and provide an evaluation of Canadian PMAs' policies regulating FCOI relationships between the associations, their membership, and the pharmaceutical industry when designing, organizing, and holding accredited CME activities. Because this is the first study of its kind, there are no evaluation tools to assess these policies. For this reason, the policy evaluation tool used in this study is original and has been developed for the purpose of this study based on the relevant literature, reviewed by three experts in the area, and pilot tested on a sample of policies from Australian medical associations.

1.3.4 Chapter 7 – Reporting of Financial Conflicts of Interest in Clinical Practice Guidelines: A Case Study Analysis of Guidelines from the Canadian Medical Association Infobase

The IOM defines CPGs as "…statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (IOM, 2011). CPGs are important tools used by physicians and other clinicians to inform screening, diagnostic, treatment, and prescribing options for their patients. It is also suggested that physicians abide by the recommendations in CPGs for legal purposes, in order to ensure that they are complying with the treatments that are recommended based on current best evidence. The recommended treatment options in CPGs are informed by systematic reviews of evidence and evaluations of the benefits and risks associated with alternative care options. CPGs are widely distributed by medical associations with the intent to provide physicians with a systematic and standardized aid to making complex medical decisions.

Although the presence of CPGs is favourable for the guidance of clinical practice for physicians, they are also currently a source of controversy. According to the IOM (2011), guidelines should be developed using a transparent and rigorous process that combines scientific evidence, clinician experiential knowledge, and patient values to enhance health care quality and outcomes. Despite this notion of how CPGs should be developed, the present state of many guidelines fails to meet these requirements. For example, a 2011 study by Todd Mendelson and colleagues (2011) found that many of the most recent guidelines by the American College of Cardiology (ACC) and American Heart Association (AHA) made treatment recommendations based on expert opinion, rather than clinical trial data. A 2012 study by Jacqueline Dinnes and colleagues (2012) found that

recommendations on “when to take action” in a sample of guidelines were based primarily on consensus statements and retrospective case studies, rather than scientific evidence. In the case of prostate cancer monitoring guidelines, the lack of a scientific systemic approach to the development of monitoring recommendations resulted from incomplete and inappropriate use of available evidence (Dinnes, Hewison, Altman, & Deeks, 2012).

This finding of inconsistencies in the use of available evidence and weaknesses in recommendations within clinical practice guidelines crosses medical fields including, but not limited to, cardiology (Mendelson, Meltzer, Campbell, Caplan, & Kirkpatrick, 2011), psychiatry (Cosgrove, Bursztajn, Krimsky, Anaya, & Walker, 2009), and urology (Dinnes et al., 2012). Concerns over validity, non-scientific, and inconsistent recommendations in guidelines are compounded by the sheer number of guidelines that are now available to doctors. For example, the Guidelines International Network (2014), serves 73 countries and houses more than 6,500 guidelines, the Agency for Healthcare Research and Quality’s National Guideline Clearinghouse houses at least 2,400 guidelines, and the Canadian Medical Association (CMA) Infobase houses over 2,700 guidelines (Bell et al., 2013). Although there is likely to be overlap in the guidelines housed by each organization, the growth in the number of guidelines available to physicians is indisputable.

Concerns about the validity, consistency, and reliability of recommendations in guidelines has generated concern amongst physicians regarding which recommendations to apply in practice (Bell et al., 2013). Despite this lack in confidence and increase in confusion about the application of these recommendations in practice, a 1997 Canadian study by Robert Hayward and colleagues (1997) found that in a sample of 1,878 physicians, confidence in guidelines was moderate or high when the guideline was issued by an official

professional medical association, as compared to the government or a third party payer. This study found that specialists felt more confident in guidelines issued by provincial colleges. Physicians without academic institutional affiliations, as compared with those with these affiliations, felt more confident in guidelines from the College of Family Physicians of Canada (CFPC). In this study, physicians were most concerned with the guideline endorsers and attached value to the authority of agencies that sponsored guidelines. The physician respondents in this study were also found to attribute additional value to guidelines that were endorsed by a respected colleague (Hayward, Guyatt, Moore, McGibbon, & Carter, 1997).

Physicians have also become concerned with the quality of guidelines because of the potential for biases within the guideline development process by guideline developers (Bell et al., 2013). Even though guidelines are advertised as being "evidence-based", scholars in this field have argued that the term "evidence" is open to interpretation. This is because the representation and interpretation of evidence can vary based on the composition of the expert panel in the guideline development group (GDG) (Guyatt et al., 2010; Spielmans & Parry, 2010). The use of GDGs that are comprised of panel members who have FCOI relationships with drug companies has generated concerns that many of the recommendations in guidelines have become vulnerable to the secondary financial interests held by panelists (Guyatt et al., 2010). These FCOI relationships have the potential to influence the development of recommendations for drug products (Guyatt et al., 2010). Moreover, the public and clinicians should trust guidelines insofar as the recommendations accurately reflect the best evidence of benefit and harms to individual patients (Ransohoff, Pignone, & Sox, 2013).

In the interest of transparency in guideline production by GDGs, the IOM has published a set of recommendations in order to strengthen their quality and trustworthiness. These recommendations include transparent guideline development and funding processes, the drastic reduction or complete elimination of FCOI relationships held by members and chairs of GDGs, and developing GDGs that accurately reflect the stakeholders (i.e., inclusion of experts, patients, clinicians, methodologists, and other researchers), and accurate portrayals, interpretations, and representations of evidence quality and recommendations. Furthermore, the IOM suggests external and public review as well as planned updates (IOM, 2011; Ransohoff et al., 2013). Justin Kung and colleagues (2012) evaluated whether 114 randomly chosen American CPGs adhered to these IOM standards and they found, in general, that the guidelines had poor compliance with the standards. Adherence to IOM standards was particularly poor in the areas of committee conflict of interest disclosures, where fewer than 50% of guidelines included disclosures. When conflict of interest relationships were disclosed, they were present for 71.4% of committee chairs and 90.5% of committee co-chairs (Kung, Miller, & Mackowiak, 2012).

Financial relationships between physicians and the pharmaceutical industry are common and well-known (Blumenthal, Causino, Campbell, & Seashore Louis, 1996; Boyd, Cho, & Bero, 2003; Chren & Landefeld, 1994; Mintzes et al., 2013; Zinner, Bolcic-Jankovic, Clarridge, Blumenthal, & Campbell, 2009), as are the effects of FCOI relationships on reporting data and prescribing decisions (Epstein et al., 2013; Rochon et al., 1994; Spurling et al., 2010; Symm, Averitt, Forjuoh, & Preece, 2006; Thomas Stelfox, Chua, O'Rourke, & Detsky, 1998). Because the express purpose of CPGs is to change clinical behaviour by presenting a synthesis of current evidence and recommendations

provided by medical experts, any biases that guideline authors exhibit as a result of their relationships with industry may be reproduced when transmitted through data to guideline readers (Choudhry, Stelfox, & Detsky, 2002; Hayward et al., 1997).

Several studies globally have determined the extent to which guideline authors have financial relationships with the pharmaceutical industry (Bindslev, Schroll, Gotzsche, & Lundh, 2013; Choudhry et al., 2002; Cosgrove, Bursztajn, & Krimsky, 2009; Langer et al., 2012; Norris, Holmer, Ogden, Burda, & Fu, 2013). The finding that guideline authors have FCOI relationships with industry is reflected across clinical areas (Bindslev et al., 2013) including cardiology (Mendelson et al., 2011), psychiatry (Cosgrove, Bursztajn, Krimsky, et al., 2009; Cosgrove, Krimsky, Vijayaraghavan, & Schneider, 2006; Cosgrove & Krimsky, 2012), urology (Dinnes et al., 2012), and diabetes control (Norris et al., 2013). In psychiatry guidelines, Cosgrove and colleagues (2006) found that 90 percent of guideline authors had at least one FCOI relationship with the companies whose products were being considered or included in the guideline.

Disclosure of varying FCOI relationships with industry in guidelines may be explained by a number of factors. It is possible that the number of physician authors engaging in FCOI relationships with industry is increasing. It is also possible that conflict of interest policies in journals in which guidelines are being published are improving, although there is still the concern that disclosures are voluntary, leading to conservative estimates of the number of COI relationships that are being reported (Bindslev et al., 2013).

There are currently no studies examining FCOI relationships in only Canadian guidelines. Therefore, it is the purpose of this study to conduct an examination of FCOI relationships disclosed by guideline authors in their guidelines. This study is based on a

sample of guidelines from the CMA Infobase, the Canadian Medical Association's database of CPGs. Because increased COI relationship disclosure is a relatively recent trend in guideline production (Mendelson et al., 2011), this study includes only guidelines that have been published or reviewed and re-approved between January 1, 2012 and November 5, 2013. Only guidelines that are provided by, and are accessible for public download, from the CMA Infobase were analyzed.

The following chapter comprises the literature review for this dissertation. The review broadly covers the literature that provides a general rationale for the necessity of institutional regulation of financial conflict of interest relationships with the pharmaceutical industry. The upcoming chapter first unpacks definitions of FCOI relationships in medicine and is followed by the justification for focusing on financial relationships in medicine. Other areas covered in the literature review include pharmaceutical industry funding and research integrity, FCOI relationship disclosures in published articles, and the destigmatization of conflict of interest.

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CHAPTER 2

LITERATURE REVIEW

2.1 DEFINING CONFLICT OF INTEREST RELATIONSHIPS IN MEDICINE

The Institute of Medicine (IOM), now the Health and Medicine Division (HMD), is a division of the National Academies of Science, Engineering, and Medicine, that operates under a congressional charter from 1863 (Health and Medicine Division [HMD], 2016a). The HMD is a private, non-profit United States (US)-based organization that provides independent, objective analyses and recommendations to encourage public policy solutions to help solve complex problems in science, technology, and medicine (HMD, 2016a). Over 3,000 volunteers offer their time, knowledge, and expertise when writing IOM reports, many of which are requested by federal agencies, independent organizations, or Congress (HMD, 2016b). In this dissertation, the terminology from the IOM, now the HMD, will be used. This body is considered to be an authoritative source for evidence-based public policy recommendations.

The IOM defined a conflict of interest (COI) relationship as "…a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest" (Institute of Medicine

[IOM], 2009). The IOM committee stressed that each of these three components, the primary interest, the secondary interest, and the conflict, are important to not only understand, but also consider, when developing effective and productive policies to mitigate such relationships. The IOM committee defined the primary interest as the purpose of the professional activity and these activities differ by profession. Physicians' primary interests include "…promoting and protecting the integrity of academic research, the welfare of patients, and the quality of medical education" (IOM, 2009). These primary interests are accepted by medical professionals when they accept their titles and act in their professional roles. Medical professionals' decisions and judgements are trusted and depended on by patients, the public, research participants, medical students, residents, and fellows for guidance that is consistent with the medical profession's primary interests (IOM, 2009).

Secondary interests, as defined by the IOM committee, are those that may exert undue influence on the manner in which or whether a medical professional exercises his or her responsibilities according to the primary interests of the profession. Financial interests need not be of great value for the influence to be reasonably considered to be undue. Whether influence is undue depends on the context and informed judgement of whether, in a particular situation, a risk of bias is unwarranted, unjustified, or inappropriate. Therefore, when any secondary interest possesses superior weight in a decision, that interest is exerting undue influence. In the context of medicine and medical professionals, secondary interests can reasonably include personal financial gain, professional advancement, recognition for personal achievements, and favours to friends, family, students, or colleagues (IOM, 2009).

Within certain parameters, financial interests are legitimate goals. Limitations must be imposed, however, when secondary interests do not remain subordinate to primary interests, including presenting medical research and scientific evidence in an unbiased manner in lectures, presentations, publications, or other means of dissemination. A COI may be formed in at least two circumstances: first, when secondary interests take precedence over and compromise primary interests, or second, a scenario in which primary interests are or will be neglected as a result of pursuing a secondary interest. The IOM committee states that "[a] conflict of interest exists whether or not a particular individual or institution is actually influenced by the secondary interest" (IOM, 2009). Similarly, Dennis Thompson (1993) and Jerome Kassirer and Marcia Angell (1993) all agree that financial conflict of interest (FCOI) relationships form as a result of a set of conditions or circumstances, regardless of whether financially benefitting from these conditions distorts physicians' work or research outcomes. Secondary interests can also influence the behaviours and judgements of professionals without their awareness. For example, gifts of both large and small value have the potential to influence decisions and may do so without the professional being conscious of the influence (Dana & Lowenstein, 2003; Grande, Frosch, Perkins, & Kahn, 2009; Grande, Shea, & Armstrong, 2012; IOM, 2009; Wazana, 2000).

Eric Campbell (2007) defines relationships with industry, at the simplest level, as "a relationship that exists whenever a physician accepts anything from a company whose products or services are related to the practice of medicine." COI relationships occur when the conditions of professional judgement concerning primary interests are influenced by secondary interests (Thompson, 1993). Primary interests are determined by the various

responsibilities assigned to professionals. Within the medical field, primary interests are considered to be ensuring patient welfare and research validity and reliability. The potential for financial gain is considered to be a secondary interest in the medical context. When secondary interests influence the primary interests of medical professionals, a COI relationship is formed. Thompson (1993) argues that although secondary interests, such as financial gain, may be necessary and desirable, these incentives must not dominate, or appear to dominate, primary interests and the related decision-making patterns and choices of these medical professionals. Thompson (1993) states that COI relationships in the medical field should be mitigated in order to prevent primary interests including patients' wellbeing, research integrity, and medical education, from being subjected to influence by financial incentives.

Marc Rodwin (1993) and Thompson (1993) both make the case that "conflicts of interest" ought not to be confused with "conflicting" or "competing" interests, which occur when a professional may face multiple interests, each of which pull the professional in different decision-making directions. Competing interests may include ethical dilemmas regarding terminating patient care, confidentiality, or using human subjects in research (Thompson, 1993). These "conflicting obligations", as explained by the IOM committee, can arise when there are two interests that can plausibly be considered to be primary. For instance, maintaining the confidentiality of a patient with a contagious disease or illness might conflict with preventing that patient from harming another individual. A physician in this situation would not be considered as engaging in a COI relationship because the interests are both legitimate and primary, and the decision to prioritize one over the other cannot be made in advance of the situation (IOM, 2009).

Blurring the line between a COI relationship and "conflicting" or "competing" interests dilutes the important distinction between the two and encourages the perspective that COI relationships are unavoidable (Thompson, 1993). Conceptualizing COI relationships is particularly important in the context of the medical field because when physicians engage in these relationships, their secondary interests and commitments may compromise their independent judgements, decision-making priorities, loyalty to their patients, and health and safety (Rodwin, 1993). This perspective is also particularly important, below, in the discussion of the perspectives of authors who seek to minimize the significance of not only FCOI relationships in medicine, but also the study of these relationships.

Kassirer deals explicitly with FCOI relationships as secondary financial interests that create dilemmas for physicians. Although Kassirer agrees with Rodwin, that COI relationships exist when physicians have dual conflicting loyalties, Kassirer further maintains that FCOI relationships are formed when physicians have competing interests that cannot be realized simultaneously and where making a personal financial choice could violate a professional code or responsibility (Kassirer, 2005). Applied to academic medical research institutions, in the current market-driven research environment, biomedical researchers are likely to find themselves proposing and pursuing research areas that are of interest to their corporate sponsors and have a high likelihood of producing commercializable discoveries (Kassirer, 2005). Although proposing and pursuing these research areas is not inherently harmful or unfavourable, commercializable discoveries may not be those that meet the primary public health needs.

Despite the implicit understanding that the primary interests of physicians and biomedical researchers should be the improvement of public health, patient health outcomes and wellbeing, university-industry collaborations tend to result in researchers' pursuing only research areas that are likely to be profitable and inconsistent with medical professionals' primary interests (Downie & Herder, 2007). Leading authorities, such as deans of medical schools and presidents of academic medical research centres, who may or may not also have FCOI relationships with industry, may find themselves in similarly enmeshed positions because they might also possess vested interests in the successes of their faculty researchers in their producing of profitable innovations and products. Simply providing faculty with opportunities to profit substantially from innovations constructs an environment that is also favourable for cultivating FCOI relationships (Kassirer, 2005).

2.2 WHY FOCUS ON FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS?

The pharmaceutical industry plays a significant role in the research, development, and commercialization of medicines worldwide. The research on, and development of medicines often involves not only the relevant drug companies, but also the hard work of faculty, researchers, and students at academic medical research institutions in universities. Research and development (R&D) produced through these university-industry linkages can be essential to the advancement of medicines; however, the FCOI relationships between medicine and industry have the potential to undermine not only the scientific process, but also the quality of information on which doctors base their clinical decisions.

Financial relationships and interactions between physicians and the pharmaceutical industry are common and pervasive (Blumenthal, 2004). These relationships may begin as early as medical or graduate school and can last the length of their careers. Furthermore, these relationships can lead to the significant risk that financial interests will unduly influence and threaten both clinical research, on which medical professionals and the public rely for guidance on treatment safety and efficacy, and professional judgements of the medical faculty and researchers who engage in such relationships (Blumenthal, 2004; Lexchin, 2005). Financial relationships between the pharmaceutical industry and medical professionals are often complex and have become the subject of heated controversy. Although it has been argued that these relationships are favourable and necessary in the advancement of medical research (Stossel, 2005), it has also been argued that these relationships are problematic because they not only control, but also impose strong limitations on the types of research that are conducted as well as on the research process, and ownership, sharing, and publishing of research data and results (Angell, 2004; Healy, 2012; Kassirer, 2005).

There are a number of types of COI relationships including, but not limited to, those that are political, religious, and financial. There are several reasons that justify the focus of this dissertation on FCOI relationships. While political and religious conflicts occur at the individual level and tend to affect that individual's interactions, companies are able to exert a much more powerful influence with financial relationships (Kassirer, 2005). Financial interests in research have increased exponentially since the 1980s as a result of legislative and funding agency priorities that promote commercial funding. Medical research is also now considered to be part of the increasingly competitive and

profitable biotechnology industry. This recognition has been reflected in initiatives, reports, and regulations produced by official organizations and governmental agencies in Canada, the United States, and United Kingdom, all of which acknowledge the potentially negative impact of financial interests on health research (Lemmens & Luther, 2007).

Financial interests are the most objective, quantifiable, negotiable, and easily identifiable (IOM, 2009; Kassirer, 2005). The financial power exerted by companies can influence multiple people simultaneously and over time and, therefore, can have a much more widespread effect. Engagement in FCOI relationships for money, prestige, obtaining research contracts, or professional advancement requires the active choice by a professional to engage in such a relationship. Furthermore, engagement in FCOI relationships is not necessary because there are alternative means by which professionals may acquire income, research contracts, or promotion. FCOI relationships can be controlled by enforceable regulations and impartial rules; whereas, to control states of mind based on subjective perceptions of political or religious beliefs is impossible (Kassirer, 2005; Thompson, 1993). Lastly, the effects of FCOI relationships on physicians' professional judgements and behaviours tend to be skewed in one direction, toward prescribing the more costly, more marketed, and less safe medications, when there are more cost-effective and safe alternatives that have been on the market for longer periods of time (Epstein, Busch, Busch, Asch, & Barry, 2013; King, Essick, Bearman, Cole, & Ross, 2013; McCormick, Tomlinson, Brill-Edwards, & Detsky, 2001).

Prescribing behaviours to do not seem to be as influenced by non-financial interests as compared to financial interactions. This may be an area for further research, but, at this point, financial interactions with industry are more predictive of prescribing

behaviour when compared with the choices made by physicians without industry interactions. Richard Adair and Leah Holmgren (2005) conducted a randomized trial to determine whether access to drug samples influenced prescribing decisions of physician residents. Twenty-nine physician residents were divided into two groups which received access to either samples of highly advertised drugs or to less expensive products, over-the-counter drugs or generics. The group of physician residents who had access to the samples of highly advertised drugs were less likely to choose to prescribe unadvertised drugs, with a pattern of use of more expensive, rather than less expensive, drugs (Adair & Holmgren, 2005). A study was conducted by Marissa King and colleagues (2013) to assess the effect of stringent policies concerning gift restriction from industry representatives. King and colleagues (2013) found an association between the prescribing choices made by physicians and the stringency of the restrictions. Physicians who graduated from medical schools with active gift restriction policies were less likely to prescribe newly marketed drugs. The length of time that medical students in this study were exposed to more stringent policies was associated with significantly lower prescribing rates once they reached clinical practice (King et al., 2013).

The trend toward increased industry funding in health research and the growing commercial focus of funding agencies undoubtedly has, and continues to, influence the health research agenda. With increasing commercial influence and focus, it is likely that research will be conducted on diseases that affect only a small proportion of the world's population. Another likely scenario to continue is that drug companies will invest in R&D for lifestyle drugs and expensive targeted therapies, which only populations in the developed world will be able to afford (Lemmens & Luther, 2007; Lexchin, 2001). It is

improbable that drug companies will dedicate R&D and resources to orphan diseases affecting a small portion of the global population unless there are enough people in the developed countries and companies can charge high enough prices for the R&D on these drugs to make it profitable for them. It is also not in the financial interests of drug companies to allocate funds to studying the impacts of non-commercial products or drug products that are no longer on-patent. Furthermore, drug companies are not required to conduct research on the long-term health effects of their products and may financially benefit from avoiding long-term follow up studies because serious adverse events (SAEs) may remain undetected or become apparent only after a long period of time (Lemmens & Luther, 2007); however, under Bill C-17 in Canada (Parliament of Canada, 2014) it is theoretically possible for Health Canada to require companies to conduct long-term studies. Whether Health Canada will actually use this legislation to require post-market studies is unknown. In some cases, drug companies have clearly failed to disclose SAEs about which they knew before patients in the general population began experiencing them and this has resulted in class action lawsuits against drug companies for harms (Bosch, Esfandiari, & McHenry, 2012; Field, 2010).

In 2009, the IOM released a report called *Conflict of Interest in Medical Research, Education, and Practice,* which called for the identification, limitation, and management of COI relationships that involve the pharmaceutical, medical device, and biomedical industries without affecting constructive collaborations with commercial industry. The IOM report identifies a series of concerns pertaining to COI relationships in medicine and subsequently provides 16 recommendations directed toward preventing bias, rather than remedying harm caused by COI relationships in medical research, education, and practice.

The IOM committee argues that financial interests must be more effectively and fairly regulated than other secondary interests (IOM, 2009). Implicitly, the IOM report uses the precautionary principle in its identification and regulation of FCOI relationships, rather than the risk assessment principle. The IOM uses the precautionary principle in the sense that it stresses the importance of preventing bias and mistrust as opposed to managing the damage after it occurs. The IOM argues that this can be done by implementing policies and procedures to maintain the integrity of scientific research, the objectivity of medical education, and the public's trust (IOM, 2009).

2.3 FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS BETWEEN PHYSICIANS AND INDUSTRY: PRESCRIBING CHOICES

Physicians and drug companies have become enmeshed in their interactions, which have become both pervasive and controversial. These relationships and subsequent flows of money from drug companies to physicians, and the resulting influence on doctors, continue to attract both public and academic scrutiny. Conflict of interest policies at medical schools, which have a duty to regulate these relationships, will be examined in chapter 3. Studies from countries around the world have shown that 80-95 percent of physicians regularly have interactions with drug company representatives. Physicians engage in these interactions, despite the research that the information provided by drug representatives is overly positive and the result is that physicians' prescribing practices are less appropriate (Moynihan, 2003). In fact, with rare exceptions, studies that have assessed physicians' exposures to information originating from drug companies have found associations with higher prescribing frequency, higher costs, and lower prescribing

quality (Grande et al., 2009; Spurling et al., 2010; Symm, Averitt, Forjuoh, & Preece, 2006).

Most practicing physicians in the United States have relationships with drug companies. A survey by Campbell and colleagues (2010) assessed the difference in the frequency with which physicians in seven medical specialties received payments from industry in 2004 and 2009. While the frequency with which physicians received payments from industry decreased from 2004 to 2009, physicians having financial relationships with drug companies remained, on the whole, in the majority. The percentage of doctors who received any drug samples, gifts, reimbursements, payments for speakers' bureaus, consulting, advisory boards, and enrolling patients in trials in 2004 was 94 percent and in 2009 was 83.8 percent (Campbell et al., 2010).

Campbell and colleagues (2010) attributed the decrease in physician-industry relationships in the United States to several factors including increased awareness and public attention by the media and professional organizations to issues of FCOI relationships. The decrease in physician engagement in FCOI relationships may also have been due to new policies adopted by some medical schools and hospitals in the United States, which have banned certain types of FCOI relationships including receiving drug samples, industry-sponsored meals, and participation in speakers' bureaus. Increased publicly accessible reporting of FCOI relationships in the United States by drug companies, medical schools, states, and the federal government may have also contributed to physicians' decreasing engagement in FCOI relationships with drug companies (Campbell et al., 2010).

Research on prescribing behaviours following industry sponsored symposia accompanied by monetary rewards illustrates that physicians' prescribing practices tend to be skewed to favour the drugs presented. A study by James Orlowski and Leon Wateska (1992) observed physicians' prescribing practices after the physicians attended all-expenses paid trips to vacation destinations for educational symposia that were sponsored by the manufacturer of the drug being presented. The impact of the trips was evaluated by tracking pharmacy inventory usage reports both before and after the symposia. Both drugs featured in the symposia were relatively new and available only intravenously. Orlowski and Wateska (1992) found that the majority of physicians who attended the symposia insisted that their prescribing behaviours were in no way influenced by accepting elaborate enticements from pharmaceutical companies. Some physicians admitted enticements might make them consider a drug that they might not have otherwise thought of prescribing, while others believed that symposia may convince them that a drug had uses or benefits for their patients that they had not otherwise considered. When the authors studied changes in physicians' prescribing behaviours before and after the symposia, they found that after the symposia, prescribing patterns significantly increased for the two drugs that were the subjects of the symposia. Importantly, these two drugs were no better than the drugs that the doctors were already prescribing (Orlowski & Wateska, 1992).

The finding that accepting items of monetary value from drug companies skews prescribing practices continues to be supported by the literature. James Yeh, Jessica Franklin, Jerry Avorn, Joan Landon, and Aaron Kesselheim (2016) conducted a study to determine the association between drug company payments to doctors and prescribing of brand-name compared with generic statins. Yeh and colleagues (2016) found that industry

payments are associated with increased rates of physicians prescribing brand-name statins and, for every US$1000 received, prescriptions of brand-name statins increased by 0.1 percent ($P<0.001$). Similarly, drug company payments for educational training was associated with a 4.8 percent increase in brand-name prescribing ($P=0.004$). Another 2016 study by Ryann Grochowski Jones and Charles Ornstein (2016) of ProPublica, a non-profit investigative journalism organization, found that physicians who received larger payments from drug companies more frequently prescribed brand-name drugs as compared with physicians who did not receive payments from drug companies. Grochowski Jones and Ornstein (2016) also found that the type of payment had an effect on prescribing. Physicians who received only meals from drug companies prescribed brand-name drugs more frequently than their counterparts who did not receive any payments from drug companies. Similarly, physicians who received payments for participating in speaking engagements prescribed brand-name drugs at a higher rate than their counterparts who received other types of payments, including honoraria, consulting fees, and travel compensation, from drug companies (Grochowski Jones & Ornstein, 2016).

A study by Barbalee Symm and colleagues (2006) looked at whether physicians' prescribing practices were influenced by the use of free sample medications in clinic X, in 2003. Clinic X, which dispensed free sample medications, was compared to clinics Y and Z, which did not dispense free sample medications. Clinics X, Y, and Z were similar in their community populations, locations, and number of physicians in the practices. All of the 23 doctors at these three clinics had equal access to formulary education, counter-drug detailing efforts such as academic detailing that relies on university or non-commercial

sources of evidence, and incentives to manage drug costs. Symm and colleagues (2006) found that clinic X physicians prescribed more costly medications per 30-day prescription than those in clinics Y or Z. Physicians in clinic X were responsible for prescribing drugs that were not included in the clinic's formulary and had the highest total prescribing costs (Symm et al., 2006).

The 2010 survey by Campbell and colleagues (2010) found that the organization of physicians' practices was related to the frequency with which physicians had financial relationships with industry. Physicians in solo, two-person, or group practices were significantly more likely to receive samples, reimbursements, and gifts than those in hospitals and medical schools; however, physicians in medical schools were the most likely to accept payments from industry (Campbell et al., 2010). Physicians who engaged in relationships with industry had a higher propensity to prescribe brand name drugs when less expensive generic alternatives were available, as compared with physicians without industry relationships who reported that they never prescribed brand name drugs when less expensive generic alternatives were available (Campbell et al., 2010).

Across primary care physicians, neurologists/psychiatrists, and cardiologists, it was observed that the more gifts that doctors accepted, the more likely they were to categorize themselves as being influenced by the interactions and this finding was statistically significant (Lieb & Brandtonies, 2010). A 2010 study on German physicians' interactions with drug representatives in their private practices found that over three-quarters of physicians had a minimum of one visit per week from drug representatives (Lieb & Brandtonies, 2010). The most commonly accepted gifts by physicians were drug samples and stationary. A small minority of physicians in the sample (4%) had not

accepted any gifts whatsoever, while the vast majority (92%) accepted drug samples either occasionally or always. Over three-quarters of doctors believed that it was often or always the intention of drug representatives to influence their prescribing practices, but only six percent of doctors thought that they were being influenced by these interactions with sales representatives and one-fifth of the doctors believed that their colleagues, not themselves, were being influenced (Lieb & Brandtonies, 2010).

Although the pharmaceutical industry claims that it provides scientific and educational information to health care professionals, expenditures on promotion to doctors are aimed at maximizing returns for both the firm and its shareholders (Spurling et al., 2010). While many physicians perceive pharmaceutical promotion to be both useful and a convenient source of information, other doctors deny that they, themselves, are influenced by drug company promotion. Some professional medical organizations have adopted the position that drug promotion ought to be subject to greater control and this has been supported by research that information provided to physicians about drugs by their manufacturers may be misleading (Hemminki, 1977; Mintzes et al., 2013; Montgomery, Mansfield, Spurling, & Ward, 2008; Othman, Vitry, & Roughead, 2009; Ziegler, Lew, & Singer, 1995).

Receiving prescribing information from drug companies does not improve prescribing choices. A review by Geoffrey Spurling and colleagues (2010) of 58 studies examined the effects of exposure to information provided directly by drug companies to doctors. They found evidence that these exposures affect physicians' quality, quantity, and cost of prescribing practices. In all studies but one (98.3%), exposure to information from drug companies was associated with either lower prescribing quality or no association was

found. Exposure to information from drug companies was also associated with increased prescribing frequency or no association was found. Three of the studies found that exposure to information from drug companies was associated with increased drug sales up to a point of diminishing returns, at which point more drug promotion became increasingly less effective (Spurling et al., 2010). In all studies but one (98.3%), physicians' exposure to information from drug companies was associated with either increased prescribing costs or no association was found. When physicians were active participants in the information exchanges at drug representatives' visits, sponsored meetings, or sponsored trials, for example, physicians more consistently had higher prescribing frequencies than when physicians experienced passive exposures to journal advertisements and mailed information. Spurling and colleagues (2010) did not find evidence supporting net improvements in physicians' prescribing practices associated with receiving information from drug companies.

Ashley Wazana (2000) conducted a systematic review of English-language articles on conflict of interest relationships and the drug industry between 1994 and 2000, plus undertook five key informant interviews. The purpose of this study was to identify the extent of, and attitudes toward relationships between physicians, drug companies, and drug company representatives as well as the effects of these relationships on the knowledge, attitudes and behaviours of physicians. Wazana found that physicians' interactions with drug company representatives were generally encouraged and began in medical school. After medical school, physicians tended to continue to see drug representatives approximately four times per month. Wazana also found that physicians' meetings with drug representatives were associated with not only those physicians'

requesting drug additions to their hospital formularies, but also changes in their prescribing choices. Other findings from the review were that when drug companies sponsored CME activities, they preferentially emphasized sponsors' drugs as compared with nonindustry sponsored CME activities and that accepting industry funding for travel or accommodations was associated with increased prescribing rates of the sponsor's drug. Physicians' attendance at presentations by drug company representatives was associated with their nonrational prescribing choices. The following associations were also found: increases in the duration of time during which physician-industry interactions occurred and increased prescribing and favourable attitudes toward industry, attending sponsored CME and increased prescribing rates of sponsors drugs, being taught by a physician drug representative and nonrational prescribing of sponsors' drugs and interactions with company representatives and positive attitudes about the interactions.

2.4 PHARMACEUTICAL INDUSTRY FUNDING AND RESEARCH INTEGRITY

The funding of research by the companies that seek to benefit from the results generates opportunities for the sponsors to influence and control research in ways that jeopardize not only research objectivity, but also its validity and reproducibility. As of 2005, the pharmaceutical industry provided approximately 70 percent of the total funding allocated to clinical trials in the United States (Mello, Clarridge, & Studdert, 2005; Sismondo, 2008). In 2004, biotechnology and pharmaceutical firms in the United States funded US$40.4 billion of the US$94.5 billion spent on biomedical research (Lexchin, 2012; Moses III, Dorsey, Matheson, & Thier, 2005). A decade later, in 2014,

Pharmaceutical Research and Manufacturers of America (PhRMA), which represents the United States' leading biopharmaceutical and biotechnology companies, reported that these industries spent an estimated US$51.2 billion on biomedical research (17.9% of total sales in 2014) (Pharmaceutical Research Manufacturers of America [PhRMA], 2015) an increase of 21.1% from 2004. Industry sponsorship of biomedical research has led to the commercialization of the scientific research process. This commercialization may deepen as clinical research is increasingly funded by industry and conducted by commercial organizations, including contract research organizations (CROs), which will be discussed in Chapters 3 and 5 (Bodenheimer, 2000).

Surveys have found that, like physicians, the majority of biomedical researchers at universities have financial relationships with industry. A survey conducted by Darren Zinner (2009) and colleagues on biomedical researchers in the United States found that the majority of researchers had relationships with industry in the past three years. The most common type of researcher-industry relationship involved consulting (31.8%), followed by paid speaking engagements (23.8%), receiving research funding as grants or contracts as principal investigators (20.1%), and memberships on scientific advisory boards (17.7%). The academic ranking of faculty researchers was strongly associated with relationships with industry. Academics with higher status tended to engage in more academic-industry relationships and this was consistent across various types of researcher-industry relationships (Zinner, Bolcic-Jankovic, Clarridge, Blumenthal, & Campbell, 2009).

Academic researchers in nonclinical research departments were more likely to have relationships with industry in upstream research and early stages of product

development through to IP licensing and the founding or managing companies. A significantly greater proportion of researchers in clinical departments (23.3%) received research grants from industry than those in nonclinical departments (9.4%). Although Zinner and colleagues (2009) found decreases in industry funding to universities, industry funds comprised a significantly greater proportion of overall research support for clinical, as compared with nonclinical, faculty members. Among the faculty receiving industry research support, it constituted almost half of all of their research funding. This industry funding was significantly higher in clinical as compared with nonclinical research departments (Zinner et al., 2009). It is clear that biomedical researchers, who may or may not be physicians, have FCOI relationships with industry throughout the stages of clinical research. Industry's increased interest in clinical, as compared with non-clinical research is clear, considering that it allocated significantly more funding to clinical research. This difference in the allocation of funds indicates industry's interest in the commercializability of biomedical clinical, rather than non-clinical, research outputs.

2.4.1 Consequences Associated with Pharmaceutical Industry Sponsorship of Research

Zinner and colleagues (2009) found, in a sample of 2,168 faculty members from clinical (n=1,071) and nonclinical (n=1,097) departments, that some faculty who received industry support for their research experienced restrictions on their permitted communications about their research as well as their choice of research. In this study, 12.9 percent of faculty produced research that resulted in trade secrets, or information that was to be kept confidential to protect its proprietary value. Zinner and colleagues (2009) also

found that when faculty were able to choose their research topics, their choices were affected either somewhat or greatly by the prospect of their results having a commercial application. Faculty with industry funding were also more likely than faculty without industry funding to report the delaying of a publication for six or more months, or that the delay of a publication was intended to prevent the publication of unfavourable results (Zinner et al., 2009). These findings are supported and complimented by an earlier study by David Blumenthal and colleagues (1996), which found similar consequences for research transparency among faculty in 1996, indicating that these problems persisted despite advances in FCOI policies.

Some scholars have expressed concerns about the potential for undue influence on research integrity when clinical studies are industry funded. Financial relationships between academic researchers and industry in the fields of biotechnology and biomedical research have faced criticism. Academic researchers who participate in these financial relationships engage in FCOI relationships, which are likely to be expressed in their research. For example, when research is industry sponsored, there is an increase in the likelihood that results that are favourable to industry sponsors are systematically selected for publication, while results that are deemed to be unfavourable to sponsors are suppressed (Bekelman, Li, & Gross, 2003).

Products tend to be systematically favoured in published research that is sponsored by the drug manufacturer (Lexchin, Bero, Djulbegovic, & Clark, 2003). A Cochrane Collaboration review of 48 studies by Andreas Lundh and colleagues (2012) found that both pharmaceutical and medical device industry sponsored studies reported more favourable efficacy results, harms results, and overall conclusions than did studies

that were funded by other sources (Lundh, Sismondo, Lexchin, Busuioc, & Bero, 2012). Lundh and colleagues (2012) found that in 14 papers, which included 1,588 drug studies, industry sponsored studies had favourable efficacy results with significant P-values more often than did nonindustry funded studies (Lundh et al., 2012).

This Cochrane review also found that two papers, which included 131 industry funded clinical trials on statins and thiazolidinediones, reported that when trials compared two drugs made by competing companies and each company sponsored a trial, the superior drug was reported to be the one made by the sponsoring company (Lundh et al., 2012). An additional paper, which included 20 selective serotonin reuptake inhibitor (SSRI) head-to-head trials, found that all 20 (100%) favoured the treatment that was manufactured by the sponsor of the trial, while none reported results that favoured the comparator drug. These findings about the relationship between sponsorship and study results are duplicated in the findings in the Cochrane report about trial conclusions. In 24 papers, which included 4,616 studies of which 4,403 were drug studies, industry sponsored studies were more likely to reach conclusions favourable to the sponsor's product (Lundh et al., 2012).

Overall, Lundh and colleagues (2012) found that industry funded studies obtained results and conclusions that were more often favourable to the sponsors' products than when studies were funded independently from industry. This review also found that when studies were industry sponsored, there were discrepancies between reported results and the wording of the conclusions, as compared with non-industry funded studies (Lundh et al., 2012). In practice, this means that the conclusions tended to overstate the benefits presented by the results. Industry funded studies were found to be just as methodologically rigorous as nonindustry funded studies when the traditional methods of measuring rigor,

i.e., use of randomized controlled trials (RCTs) or blinding, were evaluated. However, evaluating only these traditional indicators of study quality may lead to missing the more subtle techniques that bias trials and lead to pro-industry results (Lundh et al., 2012).

2.4.1.1 Publication Bias or Selective Publication

Several biasing techniques that drug companies use to ensure that their studies yield favourable results have been identified in the literature. Publication bias, or selective publication, is a well-known consequence of drug companies both conducting clinical trials and owning the results from them. Publication bias refers to the likelihood that studies with favourable results are more likely to be published than studies with results unfavourable to the sponsor (Fries & Krishnan, 2004). Some estimate that clinical trials with favourable results are twice as likely to be disseminated as trials with unfavourable results (Goldacre, 2013). Those with significant results are also more likely to be published, sometimes more than once (Schott et al., 2010). The magnitude of publication bias is controversial because the only way to establish whether trial results have been hidden is if it is known whether the trials were conducted in the first place. Although there have been global efforts for clinical trial registration, there are still inconsistencies in the registration of trials and it has been estimated by Ben Goldacre that around 50 percent of all clinical trials for currently used drugs remain unpublished (Goldacre, 2013).

In 2004, the 11 leading medical journals that comprised the International Committee of Medical Journal Editors (ICMJE) imposed the requirement that by 1 July 2005 clinical trials had to be registered in order to have their results published in the

journals. Similarly, in January 2005, major pharmaceutical manufacturer organizations including PhRMA and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) adopted guidelines that required their members to enter trials prospectively into publicly accessible registries. Despite these wide-reaching requirements for trial registry, some data suggests that pharmaceutical companies are still failing to register important information on clinical trials (Law, Kawasumi, & Morgan, 2011; Prayle, Hurley, & Smyth, 2012) and at the same time these trials are being published in journals that are members of the ICMJE (Mathieu, Boutron, Moher, Altman, & Ravaud, 2009).

Although many journals subscribe to ICMJE guidelines for trial registration and require a registration number for publication, some journals continue to use vague language to prospective authors concerning trial registration such as "[w]e encourage the registration of all interventional trials" (Mathieu et al., 2009). This unclear language in journals' policies may help to explain both inadequate trial registration and lack of adherence to trial reporting guidelines (Mathieu et al., 2009). Although the ICMJE's implementation of this requirement led to a sharp increase in trial registration in ClinicalTrials.gov, information provided by the companies on trial characteristics and protocols, including primary endpoints, remained either imprecise or absent (Schott et al., 2010).

Licensing studies are important in the assessment of new drugs, which are carried out almost exclusively by drug companies. In comparisons of data provided to the FDA versus that which has been published in medical journals, findings show that approximately 25 to 50 percent of studies submitted for licensing purposes remain

unpublished. Studies with favourable and significant findings are statistically significantly published more often than studies that have produced either unfavourable or non-significant findings. In other cases, negative or unfavourable results were portrayed as positive or favourable findings. For example, a study on SSRI trials found that trials with significant results were not only more likely to be published, but also to be published more than once. By contrast, SSRI trials with unfavourable or non-significant results were not published (Schott et al., 2010).

2.4.1.2 Design Bias

Design bias, mentioned above, is another strategy utilized by pharmaceutical companies to ensure favourable results in their trials. Design bias occurs before a clinical trial has begun, when the trial parameters and protocols are being determined, but before the final decision to initiate the trial has been made. Trial design is important to companies because only drugs that continue to show promise through the drug development sequence including pharmacological studies, pharmacokinetic studies, animal studies, initial human studies, dose ranging studies, and toxicity studies, among others, reach the stage where they can be tested in RCTs. When drugs reach the RCT stage, there is already a great deal of information known about these drugs (Fries & Krishnan, 2004).

Drug companies, which sponsor and run their own clinical trials, ‘design for success’ within well-established procedures wherein company consultants and employees engage in debates about what is known about the drug, its competitors, its potential toxicity or efficacy advantages, and the potential disease indication for the drug. It is only

following these discussions that clinical trials are designed. The process of designing a clinical trial involves considering patient populations, dosages, study duration, end-points, and comparators that are likely to provide a positive results for the sponsor. Also considered in study design is its acceptability to the FDA. Theoretically, design bias is not in itself a problem because drugs with promise should be studied in a way that identifies their therapeutic niches (Fries & Krishnan, 2004); however, in practice, problems with bias arise when the sponsor has a direct role in designing, monitoring, and reporting results of a study from which it seeks to gain revenue and in which it has invested potentially hundreds of millions of dollars.

2.4.1.3 Sponsor Control over Clinical Trial Protocols and Data Analysis

Execution of clinical trials according to *a priori* protocols, as well as the objective interpretation and publication of results, can also be influenced through agreements and contracts that stipulate that the sponsoring drug company has access to trial data or that give it the power to restrict or prevent publication of the results (Schott et al., 2010). There are a number of different stages and characteristics of clinical trials that are influenced by drug company sponsorship. For example, internal industry documents have provided evidence that drug companies have failed to reveal relevant data on adverse drug reactions (ADRs) to the public or the FDA at the appropriate times. For example, the manufacturer of cerivastatin was aware of the drug's interaction with gemfibrozil, which lead to an increased occurrence of rhabdomyolysis (muscle breakdown), approximately 100 days after the product was launched on the market. It took 18 months, however, for this interaction to be added to cerivastatin's product information on contraindications. Another

example is that the manufacturer of rofecoxib had data on increased mortality in Alzheimer's dementia patients, but failed to communicate this to both patients and the FDA in a timely manner. The manufacturer of rofecoxib also failed to adequately evaluate the occurrence of cardiovascular ADRs (Schott et al., 2010). Physician and FDA official, David Graham, testified on the harms data for rofecoxib and estimated that approximately 100,000 excess cases of heart attack and sudden cardiac death occurred (Graham, 2004).

The manufacturer of paroxetine (Paxil) failed to include known ADRs in the drug's accompanying information. A 2008 study by Ivar Aursnes and Marianne Klemp Gjertsen explored the ADRs that had already been documented at the time that paroxetine was first licensed in 1989 (Aursnes & Klemp Gjertsen, 2008). The authors gained access to the 1989 clinical data on paroxetine that was presented to drug agencies globally (Aursnes, Tvete, Gassemyr, & Natvig, 2005) after an unusual decision by the Norwegian Civil Ombudsman that the Ministry of Health should permit them to examine these documents. Out of 32 ADRs that the test group reported, only eight were listed as common, despite 19 of the 32 ADRs being statistically significantly more common in the test group compared to the control groups. As of 2008 when this study was published, five of these 19 ADRs were still not mentioned in the Summary of Product Characteristics (SPC), which accompanies Patient Information Leaflets (PILs) for licensed medicines in Europe (Aursnes & Klemp Gjertsen, 2008). Included within these five unlisted ADRs were paresthesia and nervousness, both of which were still not mentioned in paroxetine's information in 2010 in Norway, over two decades after the findings were first known (Schott et al., 2010).

A 2015 research study by Joanna Le Noury and colleagues re-analyzed SmithKline Beecham's (now, GlaxoSmithKline, GSK) Study 329 on the safety and efficacy of paroxetine compared to imipramine, to determine whether access to and reanalysis of the full data set from a RCT would result in different findings than in the study originally published in 2001 (Le Noury et al., 2015b). Le Noury and colleagues gained access to 77,000 pages of de-identified case report forms (CRFs). They found that neither paroxetine, nor imipramine proved to be effective when it was used to treat major depression in adolescents. In their re-analysis, they also found a clinically significant increase in harms with both imipramine and paroxetine (Le Noury et al., 2015b). These findings are extremely important because they both contrast with the originally reported and interpreted results in the original 2001 publication. Le Noury and colleagues also found that the original study employed biasing techniques in the coding of adverse events in the study, which masked important differences in the suicidal behaviours of the original participants in the study. The decision-making trail, made available by Le Noury and colleagues in Box 2, Appendix 3 (Le Noury et al., 2015a), leads the readers to the unexplainable coding choices made by the original Study 329 team. These coding choices transformed serious adverse events, such as intentionally swallowing 80 Tylenol tablets, into the misrepresentative and completely minimized category of "emotional lability" (Le Noury et al., 2015b).

As the above example shows, techniques used by companies to bias study outcomes are both complex and comprehensive and are utilized at every level of the drug evaluation process, making them exceptionally difficult to detect (Lexchin, 2012). Some additional techniques include enrolling healthy patients in phase III trials, purposefully

administering an insufficient dose of the test or comparator drug, and testing the experimental drug against placebo when there are active medication alternatives on the market (Bero, Oostvogel, Bacchetti, & Lee, 2007; Chopra, 2003; Rochon et al., 1994).

2.4.1.4 Use of Composite Endpoints

Industry funded clinical trials have also been known to use composite outcomes and alter primary endpoints to achieve favourable results (Cordoba, Schwartz, Woloshin, Bae, & Gotzsche, 2010; Lim, Brown, Helmy, Mussa, & Altman, 2008; Schott et al., 2010). For example, the efficacy of gabapentin for off-label indications was inflated by altering the primary endpoint in a study and also ensuring that unfavourable data remained unpublished (Schott et al., 2010).

Use of composite outcomes in clinical trials can provide an overall estimate of the effect of a drug intervention (Cordoba et al., 2010). Using composite outcomes also allows investigators to assess more than one aspect of a patient's health status by allowing reporting on more than one outcome and reductions in sample size requirements with the latter reducing costs and time (Cordoba et al., 2010). However, composite endpoints can be manipulated, and this potential is sometimes used by drug companies to inflate the appearance of the benefit of their products (Cordoba et al., 2010). To determine how composite outcomes were used in published clinical trials in medical journals, Cordoba and colleagues (2010) conducted a systematic review of RCTs and found that the use of composite outcomes in clinical trials is problematic for a number of reasons including that they conflate adverse events that are not equal, for example, chest pain and angina.

Composite endpoints use has been characterized by a lack of rationale explaining how they were constructed, inconsistent and unclear reporting, *post hoc* changes to the composite outcomes when these outcomes should be determined prior to data collection, and cherry picking of favourable outcomes or combinations thereof.

Cordoba and colleagues (2010) also note their encounter of "…the most ingenious way of getting rid of dead patients that [they had] ever seen" by way of composite endpoints. They noted that, "[d]eaths in a cardiovascular trial were listed only if they occurred before anything else. Thus, one might avoid deaths by including a component that precedes death, such as chest pain". In this case, the component of the composite outcome considered in the analysis was not death, but chest pain.

The authors found that components of composite outcomes are often inadequately reported and characterized by a "lack of logic" that inflates the appearance of a drug's safety and efficacy (Cordoba et al., 2010). Another concern was that the definitions of the composite outcome changed from the abstract, to the methods, to the results sections of the published papers, indicating that the investigators chose which data to target in their analyses (Brody, 2011; Cordoba et al., 2010). An additional problem that Cordoba and colleagues (2010) found was that readers tended not to be reminded throughout the published trials about which components of the composite outcome had improved, with the article stating only that the overall composite outcome had improved. It is often difficult to explain or understand the true meaning of an effect on a composite outcome, which is why its allowance by the most highly regarded general medical journals is important to note. The misuse of composite outcomes and their widespread use within medical journals likely leaves many readers confused and with an exaggerated perception

of the safety and efficacy of drug interventions, which is why Cordoba and colleagues (2010) and Brody (2011) recommend avoiding the use of composite outcomes.

2.4.1.5 Seeding Trials: Use of Post-Market Surveillance Studies (Phase IV Trials)

Even after clinical trials have been conducted, drugs have been approved, physicians are prescribing the drugs, and patients are taking the drugs, pharmacovigilance must still be conducted. For the duration of the patent, manufacturers that have a financial interest in the success of the drug want to maintain the drug's reputation to ensure its continued use. There are clear examples of efforts taken by companies to protect their profits, despite known drug harms that had been revealed during clinical trials. As stated earlier, in Canada, Bill C-17 theoretically gives Health Canada the authority to require post-market trials, but it is unclear if Health Canada will use this authority in practice (Parliament of Canada, 2014). In the United States, the FDA can mandate post-market trials under certain conditions (Schultz, 2007); however, industry is also known to misuse phase IV trials through a strategy called seeding trials.

A "seeding trial" is a clinical study that operates under the guise of testing a scientific hypothesis, but in fact is intended as a marketing trial to make the drug known to prescribing physicians in order to increase its sales (Goldacre, 2012; Schott et al., 2010). Seeding trials occur when drug companies sponsor and run a trial involving hundreds of physicians who recruit only a few patients each. Drug companies sponsor seeding trials not to obtain high-quality scientific information, but to change the prescribing habits of many physicians in a relatively short period of time (Sox & Rennie, 2008). Physicians

agree to be involved in these trials because they feel flattered that the sponsor considers them to be key opinion leaders (KOLs) and inflates their status as research team members by providing them with the title of investigator. These chosen physicians are, then, paid by the drug company by way of consulting fees to advise the company on the use of the drug, plus an additional payment for each patient that they enroll. The result is that these physicians become invested in the future success of the drug and praise the drug to their medical colleagues and patients. The physician, perhaps unknowingly, becomes an integral part of the drug company's marketing team (Sox & Rennie, 2008).

Some documented seeding trials include ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness) sponsored by Merck & Co. (Hill, Ross, Egilman, & Krumholz, 2008) and STEPS (Study of Neurontin: Titrate to Effect, Profile of Safety) sponsored by Parke-Davis (previously a division of Warner-Lambert Co., now a subsidiary of Pfizer Inc.) (Krumholz, Egilman, & Ross, 2011).

The ADVANTAGE trial was determined to be a seeding trial through analysis of internal and external Merck & Co. correspondence, reports, and presentations between 1998 and 2006 (Hill et al., 2008). In January 1999, prior to the launch of Vioxx (rofecoxib), Merck & Co.'s marketing division developed the ADVANTAGE clinical trial. The marketing division neither revealed the promotional intent of the trial, nor its involvement in the trial. Rather than disclose the promotional purpose of the ADVANTAGE trial, the marketing division informed physician-investigators, trial participants, and institutional review board (IRB) members that the purpose of the trial was to measure the gastrointestinal safety of Vioxx. In total, there were 600 physician-

investigators and a total of 5,557 patients enrolled in the trial (n=2,785 patients with osteoarthritis assigned to Vioxx; n=2,772 patients assigned to naproxen) for a three-month trial that began approximately two months prior to Vioxx receiving market approval by the US FDA on 22 May 1999 (Hill et al., 2008). Hill and colleagues (2008) located a slide by Merck & Co.'s marketing division, which stated that the primary goal of the ADVANTAGE trial was for the physician-investigators to "[g]ain experience with Vioxx prior to and during the critical launch phase [of Vioxx]". The ADVANTAGE trial was developed by the marketing division with a marketing objective, the division was responsible for collecting, analyzing, and disseminating both the scientific and marketing data that emerged from the trial, and Merck failed to reveal the true purposes of the trial to its participants, physician-investigators, and the IRB that granted ethics approval for the trial (Hill et al., 2008). The ADVANTAGE trial was used by Merck & Co. to illustrate the value of Vioxx to the physician-investigators, to carefully and precisely integrate its marketing staff into trial-related operations and vice versa, and to track the physician-investigators' prescribing of Vioxx (Hill et al., 2008). The ADVANTAGE trial was published in Annals of Internal Medicine in 2003 as a randomized controlled trial and remains available online (Lisse et al., 2003).

The STEPS trial was determined to be a seeding trial through an examination of all documents, including company internal and external correspondence, reports, and presentations between 1990 and 2009, as well as other legal documents released in litigation (Krumholz et al., 2011). These documents provided evidence that STEPS was a seeding trial that was postured as a legitimate scientific study. The STEPS trial was a phase IV uncontrolled and unblinded clinical trial that was sponsored by Parke-Davis. Informed

consent documents show that the 2,759 participants, who were assigned to 772 physician-investigators, were told that the stated purpose of the study was to determine the safety, efficacy, tolerability, and quality of life of participants who received gabapentin (Neurontin) without mentioning its marketing intent (Krumholz et al., 2011). The scientific validity and poor trial design was questioned by two institutions: The Johns Hopkins University IRB rejected the application and, subsequently, rejected it again on appeal because the IRB members disapproved of the protocol, which they believed to be "…too vague to allow any scientific conclusions to be reach[ed]" (Krumholz et al., 2011). The opinion of the FDA director of the Division of Drug Marketing Advertisements and Communications (DDMAC) was that the STEPS trial was favourable from a marketing perspective, but was not justifiable for obtaining data on high dose use (Krumholz et al., 2011).

The quality of the data obtained during the STEPS trial was undermined by poor clinical trial conduct. Parke-Davis not only recruited physician-investigators with little or no clinical trial experience and did not provide sufficient training or audit study sites prior to the beginning of the trial, but also had its data "cleaned up" and analyzed by a CRO (Krumholz et al., 2011). In correspondence with the Medical Scientific Affairs Senior Assistant Clinical Scientist at Parke-Davis, the CRO indicated that "the data clean-up process for STEPS has been a larger task than anticipated. The data was very dirty" (Krumholz et al., 2011). The CRO then provided a strategy and choices of scenarios for cleaning up the data (Krumholz et al., 2011). Parke-Davis's planned marketing strategies relied heavily on STEPS as a key deliverable for positioning the drug to neurologists and primary care physicians as "the safe and easy add-on" for noncompliant seizure patients

(Krumholz et al., 2011). In internal marketing memos, the STEPS trial was referred to as "…the best tool [Parke-Davis] has for Neurontin and we should be using it wherever we can" (Krumholz et al., 2011). The STEPS trial resulted in two articles published in *Epilepsy* (McLean et al., 1999) and *Seizure* (Morrell et al., 2000) and both published articles are still available online.

It is important to note that drug companies may use a combination of these strategies to ensure favourable outcomes. Published data may be the result of a number of complex and layered industry tactics aimed at shaping research data and the medical literature base.

2.5 FINANCIAL CONFLICT OF INTEREST DISCLOSURES IN PUBLISHED MEDICAL RESEARCH

Conflict of interest disclosures are now commonly required upon publishing articles, including clinical practice guidelines, in medical journals. Therefore, researchers have been able to assess the frequency with which authors possess and disclose FCOI relationships.

2.5.1 Financial Conflict of Interest Disclosures and Results Published in Journal Articles

Clifford Perlis and colleagues (2005) conducted a study that evaluated the extent and impact of FCOI relationships between authors and drug companies in 179 clinical trials published in the four highest impact dermatology journals. They found that studies

that named authors with disclosed FCOI were more likely to report a positive result. Roy Perlis (2005) and colleagues conducted a study on clinical trials published in the four highest impact psychiatry journals. They found that regardless of funding source, all studies by authors who had FCOI relationships were significantly associated with positive trial outcomes.

Henry Stelfox and colleagues (1998) analyzed whether there was an association between authors' positions on the safety of calcium-channel antagonists in published literature and their FCOI relationships with drug companies. In addition to analyzing the published positions of these authors, Stelfox and colleagues also surveyed them to obtain information about their FCOI relationships with pharmaceutical companies to assess FCOI relationships that potentially were not disclosed in the journal articles. Authors' FCOI relationships were statistically significantly associated with their published support of calcium-channel antagonists (Stelfox, Chua, O'Rourke, & Detsky, 1998). Stelfox and colleagues also found that authors with published support for calcium-channel antagonists were statistically significantly more likely to have FCOI relationships with not only manufacturers of calcium-channel antagonists, but also any pharmaceutical manufacturer.

2.5.2 Financial Conflict of Interest Disclosures and Results Published in Clinical Practice Guidelines

Niteesh Choudhry (2012) and colleagues found, through a survey of guideline authors, that the vast majority reported having a relationship with industry. These relationships ranged from receiving funding, honoraria and support for educational programs to being employed by and owning equity in drug companies. Fifty-nine percent

of these authors also reported FCOI relationships with drug companies whose products were considered or included in the guideline that they authored. Despite the high number of FCOI relationships reported in the survey, these authors did not disclose their FCOI relationships in 42 of the 44 guidelines that they authored. In only 1 out of the 44 guidelines in this study, did all authors declare that they held no FCOI (Choudhry, Stelfox, & Detsky, 2002). In a systematic review by Susan Norris and colleagues in 2011 on 12 guidelines, authors on all 12 guidelines disclosed FCOI relationships with the pharmaceutical industry (Norris, Holmer, Ogden, & Burda, 2011).

Lisa Cosgrove and colleagues (2006) conducted a study that examined the financial interests of the panel members responsible for revisions of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*. They decided to use the term "financial interests" rather than COI relationships because they stated that the term COI relationship implies an interpretation of the interest. Instead, the authors defined categories of financial interest to include real, perceived, or potential COI relationships. The *DSM* is the leading medical manual used in the diagnosis of psychiatric disorders. *DSM* panel members have a significant influence in the determination of whether new psychiatric diagnoses should be added to the manual, or alternatively, whether older diagnoses should be revised in the next edition of the manual (Cosgrove, Krimsky, Vijayaraghavan, & Schneider, 2006).

For 170 expert panel members on the *DSM-IV*, the authors screened for any financial affiliations that they had with the pharmaceutical industry between 1989 and 2004 by gathering data from published papers or through Internet search methods. Ninety-five of the 170 panel members (56%) had one or more financial interests with drug companies. More than 80 percent of expert panel members on six out of 18 panels had

financial interests in pharmaceutical companies, while 100 percent of the experts on two of the 18 panels had financial interests with pharmaceutical companies (Cosgrove et al., 2006).

Brian Pilecki (2011) and colleagues provided an analysis of financial interests of the 29 *DSM-V* task force members whose potential COI relationships at the time of the study were published on the *DSM-V* website. Of the 29 task force members, 21 (72%) disclosed at least one financial interest with any pharmaceutical, healthcare or insurance, or biotechnology corporation, resulting in 220 ties (range: 2 to 22, mean: 9.6). When multiple ties to individual corporations were considered, the number of financial ties rose to 278. Of the 29 task force members, 19 (66%) disclosed at least one association with a drug company, resulting in 114 associations with drug companies (Pilecki, Clegg, & McKay, 2011).

In 2012, Cosgrove and Krimsky (2012) added to the study by Pilecki and colleagues (2011) by also considering the 141 expert panel members who made up 13 *DSM-V* teams. In total, there were 170 *DSM-V* members (29 task force members + 141 panel members = 170 total *DSM-V* members). Sixty-nine percent of the *DSM-V* task force members disclosed financial ties with drug companies, representing a relative increase of 21 percent in those with financial ties to industry since the *DSM-IV*. These authors also found that in both the *DSM-IV* and *DSM-V*, the panels with the most members with FCOI relationships with drug companies recommended pharmacological treatments as first-line interventions (Cosgrove & Krimsky, 2012).

A study by G. Michael Allan and colleagues (2015) was conducted in order to determine the professions of guideline contributors, as well as whether those professionals

disclosed conflict of interest relationships through disclosure statements within primary care guidelines. They assessed 296 guidelines from the family medicine section of the Canadian Medical Association (CMA) Infobase. Of these guidelines 100 were excluded because they had limited relevance or were duplicates and an additional 20 guidelines were excluded because they did not provide information on contributors, which Allan and colleagues (2015) defined as authors and committee members. A total of 2,495 contributors were assessed. Of these contributors, 1,343 (53.8%) were non-family physician specialists, 423 (17.0%) were family physicians, 141 (5.7%) were nurses, 75 (3.0%) were pharmacists, 269 (10.8%) were other clinicians, 203 (8.1%) were non-clinician scientists, and 41 (1.6%) were unknown professions.

In general, Allan and colleagues (2015) found that approximately two-thirds of the guidelines did not provide conflict of interest disclosures for their contributors. In this study, 32.8 percent of contributors who provided conflict of interest disclosures had at least one conflict of interest relationship. Non-family physician contributors outnumbered physician contributors in both industry and non-industry funded guidelines, but in non-industry funded guidelines a higher proportion of contributors were family physicians. Non-family physician contributors were the most likely to report conflict of interest relationships (48.6%), as compared to pharmacists (30.0%), family physicians (27.7%), nurses (9.9%), non-clinician scientists (9.6%), and other clinicians (2.9%). Allan and colleagues (2015) recommend that there be a balance professional representation within guideline contributors and that the participation of contributors who have conflict of interest relationships with industry should be minimized.

2.6 THE DEREGULATION OF FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS IN MEDICINE: EFFORTS TO DESTIGMATIZE FINANCIAL CONFLICT OF INTEREST AND DELEGITIMIZE ARGUMENTS IN FAVOUR OF REGULATION

Despite the established literature base that continues to conclude that there are associations between FCOI relationships, published research, and physicians' prescribing choices, efforts by some physicians to delegitimize this research persists using a set of common strategies. Some of these strategies will be both addressed and refuted in this section.

2.6.1 Focusing Too Narrowly: Taking a Step Back to Assess the Effects of Financial Relationships with Industry

Arguments against regulating conflict of interest relationships tend to focus too narrowly on the specificities of the relationship itself and not on the effects that these relationships tend to have more broadly. A physician who argues against strict regulation for FCOI relationships is Thomas Stossel, who is a senior physician in the Hematology Division at Brigham and Women's Hospital, visiting scholar at the American Enterprise Institute (AEI), and American Cancer Society Professor of Medicine at Harvard Medical School (American Enterprise Institute [AEI], 2015). His work on conflict of interest relationships in medicine seeks to establish that arguments to regulate these relationships are informed by the myth that regulating COI undermines medical innovation (Rago, 2015; Stossel, 2015). Stossel has framed this argument in the following way:

> What the conflict of interest movement does not yet regulate it maligns. It demonises 'speakers' bureaus,' which organise doctors to provide company sponsored education, and ghostwriters, accusing professional writers hired by

> companies of routinely creating promotional fiction that is allegedly legitimised by honorary academic authors (Stossel, 2008b).

Counter to this claim, the "conflict of interest movement" asks critical questions about these relationships and the effects that they have. For example, with regards to speakers' bureaus and company sponsored medical education, the issue is not necessarily with the act of speaking. The issue lies in the carefully planned nuances that make it worthwhile for companies to be spending money on these activities. Speakers' bureaus and company sponsored medical education events are often used as physician-to-physician environments in which companies can identify and train strong pharmaceutical industry advocates and expand their rolodex of speakers and KOLs or thought leaders. When physicians engage in industry funded speaking relationships, they can be paid US$2,500 to US$3,000 for delivering a single lecture, based on a lecture or slide-deck that was developed by the sponsoring company. Furthermore, company sponsored medical education has become big-business in which agencies called medical education communication companies (MECCs), are contracted by pharmaceutical companies, to produce educational and communications materials and organize grand-rounds lectures at hospitals, train KOLs, create their lectures and manage their speakers' bureaus, and organize a number of live events including satellite symposia, podcasts, conferences, and advisory board meetings (Elliott, 2004). MECCs promote their abilities to provide "promotion through education" and that this 'education' can be "custom tailored to meet the pharmaceutical marketers' needs" (Sismondo, 2011). These relationships, among others including ghostwriting, their relevance to conflict of interest regulation, and the effects of these relationships will be explored in Chapter 5.

2.6.2 Public versus Private Innovation Successes

Authors who oppose conflict of interest regulation also tend to make overstatements without concrete data to support their assertions regarding the effects of private industry on research. One example of such a statement made by Stossel argued in favour of decreased regulation of private industry by overstating the broad successes of private industry:

> All of these charges obscure the fact that only private companies bring new products to patients and that medical care has improved steadily and spectacularly because of them. Fraud and pathological bias could never have conferred these monumental achievements (Stossel, 2008b).

Private companies bring products to market because in the current structure of R&D, upstream research tends to be conducted by researchers in academic institutions. As a response to state budgetary cutbacks, university funding has been constrained, which has led to the restructuring of funding schemes for research and education. As a direct result of increased industry support for academic operations within universities, the biotechnology and pharmaceutical industries have adopted influential roles through university-industry partnerships. These partnerships have led to an increased focus on biomedical research and innovation (Krimsky, 2004). This restructuring has paved the way for more private sector funding to be siphoned into universities. Once university-based research outputs reach the point at which they can be commercialized, the companies that funded the research take possession of them and pursue their commercialization for profit, rather than primarily using them to further academic interest or public good (Kenney, 1986; Slaughter & Leslie, 1997).

The claim about private industry's capabilities as the only provider of new medical technologies to patients must be considered in the context of the absolute number of drugs approved for market and the percent of these that are true therapeutic advances. The pharmaceutical industry and its analysts define and measure innovation in terms of the number of New Molecular Entities (NMEs) in the US and New Active Substances (NASs) in Canada that are approved, rather than how many of these NMEs result in therapeutically superior new medicines. The US Food and Drug Administration (FDA) defines NME as "…an active ingredient that has never before been marketed in the United States in any form" (US Food and Drug Administration, 2012). Health Canada defines NASs as drugs that contain "…a medicinal ingredient not previously approved in a drug in Canada and that is not a variation of a previously approved medicinal ingredient" (Health Canada, 2015).

Historically, researchers in public-sector research institutions (PSRIs) have been known to perform the upstream, basic research, while corporate researchers have conducted the downstream, commercializable research which has led to the development of drugs for the market. Ashley Stevens and colleagues (2011) conducted a study to determine the role of PSRIs in the applied stages of drug discovery. They identified 153 drugs that were approved by the US FDA between 1970 and 2009 that had originated from public-sector research. These 153 drugs received 203 new-drug or biologics indications. Stevens and colleagues (2011) noted that while the 153 drugs ranged across therapeutic categories, perhaps the most notable was the large number of vaccines because the majority of the important and innovative vaccines captured in this study were developed by PSRIs.

Despite measuring industry success by the number of new drugs brought to market, the majority of these new drugs offer relatively very few clinical advantages compared with existing treatments already on the market (Light & Lexchin, 2012). For example, between 1978 and 1989, only 34 out of 218 (15.6%) drugs approved by the US FDA were determined to be important therapeutic gains. Another report found that between 1974 and 1994, only 11 percent of drugs approved for market were considered to be therapeutically and pharmacologically innovative (Light & Lexchin, 2012). Independent reviews of new drugs approved between the mid-1990s and mid-2000s by Health Canada (Morgan et al., 2005), the FDA (Angell, 2004), and the European Medicines Agency (EMA) (Motola et al., 2006; van Luijn, Gribnau, & Leufkens, 2010) show that 85 to 90 percent of all new drugs approved for market were considered to provide few or no clinical advantages to patients over drugs already on the market (Light & Lexchin, 2012). Therefore, the true innovation crisis is that even with significant spending on R&D in the private sector, for the most part, only drugs with minor variations or drugs with equivalent or inferior clinical measures have been submitted and approved for marketing (Light & Lexchin, 2012).

Other counterarguments to regulating COI relationships are that "…public investment enjoys huge return, and the solid conclusion is that society benefits disproportionately from having academic physicians and scientists participate in product development" (Stossel, 2008a). This argument must be considered in the context of public funding and private profit. Public funding plays an extremely important role in upstream research in the discovery of both drugs and vaccines. Of course, it is beneficial for academic physicians and scientists to participate in product development, but the public benefits from only the discoveries that private industry deems to be commercializable.

Traditionally, there has been a clear boundary between the roles of the public and private sectors in research concerning the development of new drugs and vaccines to meet the needs of the population (Stevens et al., 2011). Publicly funded research tends to lead to drug and vaccine discoveries that are anticipated to have disproportionately important clinical effects. Furthermore, both upstream and downstream research that is conducted in the public sector has had a more immediate effect on the improvement of population health than was previously recognized (Stevens et al., 2011).

Much of the upstream research, which tends to be conducted at academic research institutions, is publicly funded. For example, between 2003 and 2007, the US federal funding sources were the largest contributors to biomedical research at academic institutions, contributing 65 percent of biomedical research expenditures at these institutions (Dorsey et al., 2010). Public funding accounts for a significant proportion of biomedical research funding, but when private industry commercializes the upstream research results, various commercial measures are imposed to protect the information that led to this product and private industry profits from public funds. Downstream research by private firms uses patenting and imposes intellectual property (IP) protection thereby making the research that comes out of academic institutions into commercially confidential information (CCI) and, therefore, the financial returns from the commercialization of the research goes not to the public that funded the upstream research, but to the firm that owns the final product.

Arguments in support of patenting suggest that strong IP protections incentivize downstream investment that is crucial to biotechnology research (Gambardella, 1995; Jensen & Murray, 2005). Those who are in favour of patenting biomedical discoveries

tend to argue that it is only through patenting that inventions can be shared globally. Alternatively, critics of patenting tend to argue that discoveries that are made on the basis of public funding should be released immediately and be made freely available in the public domain, rather than be exploited for commercial gain. This is because the most important biotechnological advancements are more likely to materialize in nonexclusive environments, rather than in environments in which only a single firm owns exclusive rights to the innovated products (Bentley, 1996). IP protection is extremely incentivized in the current research environment and is a source of profit and prestige for both universities and biotechnology corporations. However, IP protection prioritizes these financial interests over not only public health and welfare, but also the ability of academics to conduct research that is free from financial interest and that contributes to the basic foundations of knowledge. Although the systemic incentivization of knowledge production and innovation has resulted in many beneficial contributions to the biotechnology and pharmaceutical sectors, it has also resulted in the centralization of knowledge so that the majority of proposed and performed research projects are in agreement with the financial interests of commercial industry.

Researchers in favour of deregulating COI relationships also highlight the putative successes of relationships with private industry and tend to follow with an example of a potentially unfavourable outcome from regulating these relationships. Lisa Rosenbaum, a physician and Instructor of Medicine at Brigham and Women's Hospital (Harvard Catalyst, 2015), criticizes proponents of conflict of interest regulation. In her three-part series (Rosenbaum, 2015a, 2015b, 2015c) published in the New England Journal of Medicine (NEJM) Rosenbaum is critical of regulating COI relationships in medicine. In

this series, Rosenbaum posits that regulating FCOI relationships between academic physicians and the biomedical industry has not been shown to improve patient outcomes and may inhibit innovation. This series by Rosenbaum seeks to cast doubt on the negative findings of the literature on conflict of interest relationships. She, like Stossel, argues that academic-industry relationships can be positive, for the most part. Stossel states that:

> By any measure, the interactions between academic research and industrial research and development, as epitomized by biotechnology, have been overwhelmingly positive. We should celebrate their achievements and protect the process that led to them. Instead, the director of the National Institutes of Health (NIH) recently abolished all corporate consulting activities by NIH researchers, and all 18,000 NIH employees must sell any investments in health-related industries … Had these rules been in force in the 1970s and 1980s, they would have prevented the scientists from making their breakthrough contributions (Stossel, 2005).

One example that Stossel provides is that academic researchers' relationships with venture capitalists led to the "immense [benefit]" of the hepatitis B vaccine (Stossel, 2005). However, the claim that "[b]y any measure, interactions between academic research and development, as epitomized by biotechnology, has been overwhelmingly positive" (Stossel, 2005) is unsupported. It is true that many of these early interactions, and even some of the current interactions, have been positive and have led to biotechnological advancements; however, these interactions must be considered within the appropriate context. Judging by the author's comments on the relationship between financial interactions with private industry and the ability of scientists to develop "breakthrough contributions", this context is therapeutic advancement and the "innovation crisis", which was alluded to earlier. Since the early 2000s, industry leaders, and policy makers have been widely stating that scientists are experiencing an "innovation crisis" in pharmaceutical research and that the pipeline for new drugs is soon to be dry. Therefore,

proponents of the "innovation crisis" argue that scientists should stop efforts to discover new drugs and instead buy into discoveries that are already in the pipeline (Light & Lexchin, 2012).

It has been argued that this version of the "innovation crisis" is a myth. Donald Light and Joel Lexchin (2012) argue that these reports promoting the "innovation crisis" are founded in the decline of the number of NMEs approved by the FDA since 1996. In 1992, legislation allowed the FDA to start charging companies large user fees when these companies submitted applications to have new drugs approved. Using this money, the FDA hired additional reviewers and was able to clear the backlog in new drug applications. It was the clearing of the backlog that produced the appearance of a decline of NME approvals in 1996. In 2005, analysts at Pfizer examined data on innovations and stated that the innovation crisis was a myth "…which bears no relationship to the true innovation rates of the pharmaceutical industry" (Light & Lexchin, 2012). Furthermore, FDA records indicate that pharmaceutical companies have produced innovations, including new biologics, at a constant rate for almost 60 years (Light & Lexchin, 2012).

2.6.3 Reliability of Company Data and FDA Advisory Board Committee members

Stossel argues that academic research and education may be less reliable than industry-originated data because industry-originated content is reviewed by the FDA:

> Purely academic research and education are arguably less reliable than their corporate or corporate sponsored counterparts. They are not, for example, subject to stringent Federal Drug Administration reporting requirements. Misconduct fells

> a single academic miscreant but can bring down an entire company (Stossel, 2008b).

Although the FDA provides more information on its approved medications than does Health Canada and has a system of public expert advisory committee hearings for new drugs that Health Canada lacks (Lexchin & Mintzes, 2004), the agency has some serious problems in terms of the relationships that its advisory board committee members have with the pharmaceutical industry. Academic physicians regularly serve on advisory committees as experts and help in interpreting scientific evidence submitted by drug companies. The FCOI relationships held by these academic physicians have the potential to influence their advisory capabilities at the FDA and on their regulatory advice (Pham-Kanter, 2014). These relationships may render the reliability of the members' interpretations and votes in advisory meetings vulnerable to the subjective financial interests of each member.

A 2006 study by Peter Lurie and colleagues (2006) examined the FCOI relationship disclosures at drug-related FDA Drug Advisory Committee meetings that took place between 2001 and 2004. Of 2,947 advisory committee members and voting consultants combined (1,957 advisory committee members, 990 voting consultants), 825 (28%) disclosed COI relationships. In 73 percent of the meetings, at least one advisory member or voting consultant disclosed FCOI relationships, but only 22 members (1%) of members were recused (Lurie, Almeida, Stine, Stine, & Wolfe, 2006). It is unclear if the members recused themselves or a committee chair recused them.

Disaggregated, 66 percent of all meetings included at least one advisory committee member with a conflict, while 53 percent of meetings that included voting consultants had at least one voting consultant with a conflict. At 14 percent of meetings, 75 to 100 percent

of advisory committee members had FCOI relationships. At 22 percent of meetings, over half of the advisory committee members had FCOI relationships. This study also examined the impact of participants' COI relationships on their voting patterns. Seventy-six out of 110 product-specific meetings met the inclusion criteria for this portion of the study. The authors found that if either advisory committee members or voting consultants with COI relationships were excluded from the votes, the results of the votes would have been less favourable to the drug in the majority of meetings, but this would not have changed the majority decision to favour or oppose the drug (Lurie et al., 2006).

The results of Lurie and colleagues' study were updated and expanded in 2014 by Genevieve Pham-Kanter (2014), who assessed whether advisory committee members voted in-line with their financial interests with industry. This study used data on voting behaviours and disclosed FCOI relationships of 1,379 unique FDA voting advisory committee members at the Center for Drug Evaluation and Research (CDER) who voted at least once between 1997 and 2011. The voting advisory meetings that were included in this study were concerned with branded products or drug classes that included branded products (Pham-Kanter, 2014).

Pham-Kanter (2014) found that the FCOI relationships disclosed by voting members varied substantially across FDA advisory committee meetings and were sometimes extensive. The median level of FCOI in these meetings was approximately 13 percent (range: 2% to 29%). On average, at least one person with a FCOI relationship was in attendance at half of the meetings. Pham-Kanter found that the most commonly reported FCOI relationship was consulting, followed by ownership equity or bonds and/or income from royalties and licenses, and research-related grants and contracts. An important and

statistically significant finding was that if a member has a financial relationship with a drug company, even if that relationship is not with the sponsor of one of the drugs on which they are voting, "…the odds are greater than 50–50 that she or he will vote in favor of the sponsor rather than against the sponsor". This means that if a member has a financial relationship with a brand name drug company, they are more likely to vote in favor of another brand name company, rather than against it, even when drugs produced by the member's brand name affiliations are not being considered in the vote.

Moreover, if members had a FCOI relationship with a sponsor, they were 1.49 times more likely to vote for the sponsor than members without FCOI relationships. If members had FCOI relationships with a competitor only, or with both a sponsor and competitor, then they were not more likely to vote in favour of the sponsor than those with no FCOI relationships. When Pham-Kanter (2014) excluded unanimous votes to analyze only non-unanimous votes, which reflected more ambiguous safety and efficacy evidence, she found that pro-sponsor bias appeared to be larger in these votes. This means that when evidence was unclear, there tended to be more pro-industry presence among the voting members. Pham-Kanter also found that the type of FCOI relationships held by members also matters. CDER advisory board committee members, who were also advisory board members for the sponsor, were much more likely to vote in favour of the sponsor.

Robert Steinbrook (2005) commented on the effectiveness of the FDA's detailed policies for balancing COI and the need for relevant expertise in advisory committee members. In a case he discussed, an FDA official stated aloud at the beginning of a meeting that because no drugs were being newly approved during this meeting and the issues being discussed were of broad applicability, "...potential conflicts of interest are

mitigated" (Steinbrook, 2005). After this meeting, it was disclosed that 10 out of 32 voting panel members had FCOI with the manufacturers of three drugs that were being considered for continued marketing. In this case, had the members with FCOI not participated in the vote, the results of the remaining committee members' votes would have been that two of the three drugs would have been removed from market (Steinbrook, 2005).

Stossel (2008b) also argues that corporate promotional information is evidence-based. However, there exists an entire literature base on direct-to-physician advertising (DTPA) (Lankinen, Levola, Marttinen, Puumalainen, & Helin-Salmivaara, 2004; Manchanda & Honka, 2005; Montgomery et al., 2008; Othman et al., 2009; Spielmans & Parry, 2010; Spurling et al., 2010; Vlassov, Mansfield, Lexchin, & Vlassova, 2001) and direct-to-consumer advertising (DTCA) (Almasi, Stafford, Kravitz, & Mansfield, 2006; Frosch, Grande, Tarn, & Kravitz, 2010; Frosch, Krueger, Hornik, & Barg, 2007; Gilbody, Wilson, & Watt, 2005; Lexchin & Mintzes, 2002; Mintzes, 2012; Mintzes et al., 2003, 2013; Wilkes, Bell, & Kravitz, 2000; Woloshin, Schwartz, Tremmel, & Welch, 2001) that disagrees with this claim and further suggests that corporate promotion fails to adequately address harms of the drugs that are being promoted. Research on the quality of corporate promotional information has found that it is often presented in such a way that benefits the sponsor. One study by Barbara Mintzes and colleagues (2013) evaluated the quality of safety information provided to physicians by pharmaceutical sales representatives in Canada, France, and the United States. This study found that there was a serious absence of information on the harmful effects of the medications promoted to the doctors by drug sales representatives and information on health benefits was provided twice as often as

information on harms. In fact, in over half of the physician-sales representative interactions evaluated in this study in three North American sites, no harmful effects were mentioned.

Even though harms information was absent in the information provided by drug sales representatives, the physicians who engaged in these interactions judged the information provided to them as positive and were willing to increase prescribing almost two-thirds of the time. Because these promotions in Canada, France, and the United States failed to include information on harms, these interactions violated national laws in all three countries (Mintzes et al., 2013). In fact, because of the mounting evidence that corporate promotional information cannot be considered to be "education", the World Health Organization (WHO) and Health Action International (HAI) developed a free handbook, available in English, French, Spanish, and Russian, for medical and pharmacy students to help them understand and respond to pharmaceutical promotion (Mintzes, Mangin, & Hayes, 2011).

2.6.4 Delegitimization of Research and Undermining the Credibility of Researchers

Some physicians take the position that FCOI relationships should be deregulated and have responded to pro-regulation researchers and their work by attempting to not only delegitimize it, but also undermine their professional credibility through the use of language and tone. In order to capture some of these individuals' perspectives, statements, ideas, sentiments, diction, and tone, this section quotes their statements and then explores them in the context of stronger regulation and enforcement of FCOI relationships.

Stossel has published several pieces arguing for the deregulation of FCOI relationships, including his book called *Pharmaphobia: How the conflict of interest myth undermines American medical innovation* (2015) and his article *Has the hunt for conflicts of interest gone too far* (Stossel, 2008b)*?* In this article, he compares those who argue for strong regulation of COI relationships to "…street evangelists urging us to repent of our sins" and notes that "most of us politely ignore [them]". Stossel further states that people who argue for this type of regulation publish "sermons" warning that medical practitioners, educators, and researchers who accept gifts or payments for services from relevant companies compromise their objectivity and calls this "…preaching by anti-business activists" (Stossel, 2008b).

Rosenbaum (2015a) refers to her experiences with outspoken medical school classmates and fellow trainees who questioned their interactions with pharmaceutical representatives and names them "pharmascolds" with "do-gooder sheen." Rosenbaum also stated that:

> This application of language associated with rape and child abuse to the circumstances of education about effective drugs reveals a feature of the conflict-of-interest movement that has fed its contagion and rendered it virtually unassailable: it casts industry interactions as a moral issue (Rosenbaum, 2015a).

Rosenbaum also judged one medical student's expression of feeling that the norms and expectations of norms in academic integrity had been violated because a professor, also a paid consultant for several drug companies, focused too much on the benefits of statins and the professor belittled a student who inquired about side effects in what was supposed to be a protected and supportive learning environment (Rosenbaum, 2015a). Expressions of misgivings by the medical student about relationships with industry may indicate not that proponents of regulating COI relationships are attempting to inject sensationalist or

condescending language into the debate, as argued by Rosenbaum, but that people experience, perhaps unexpected, reservations concerning medical information that originates from industry. Nevertheless, proponents of deregulation of FCOI relationships need not resort to extremes of providing judgements about individuals' characters or opinions about COI relationships. Moreover, proponents of regulation need not be labelled as "activists", "anti-business", "pharmascolds", or having "do-gooder sheen" to reasonably expect and freely promote concepts that, on the whole, ensure the integrity of the medical profession and patient welfare should be prioritized over secondary financial interests.

It is difficult to come to any research conclusions with certainty; however, when considered together, the published literature on COI relationships certainly draws concrete associations between engaging in these relationships and shifts in professional behaviours and judgements in both academic biomedical research and regulatory capacities, as well as conclusions from academic biomedical research. Informed by the preceding literature review, the following section provides an analysis of a policy update from an institution that regulates physicians in Ontario to provide a case study of changes in the environment of FCOI relationship regulation.

2.7 FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS IN PRACTICE: AN INTRODUCTORY ANALYSIS OF THE COLLEGE OF PHYSICIANS AND SURGEONS OF ONTARIO POLICY ON INDUSTRY INTERACTIONS

The CPSO (n.d.-a) is responsible for regulating the practice of medicine for doctors in Ontario in order to protect and serve the public interest. To accomplish this, under

Ontario provincial law, physicians have been granted a degree of authority to self-regulate through the CPSO. In order to practise medicine in Ontario, all physicians in Ontario are required to be members of the CPSO. According to the CMA (2015), Ontario's concentration of physicians is the highest of all Canadian provinces at 35.3 percent of the doctors in Canada. Because of Ontario's proportionately larger physician population, it is worthwhile to present a comparative policy case study analysis of the CPSO's 1992 policy with its updated 2014 policy which dictated and now dictate, respectively, the standards for FCOI relationships for the CPSO's membership.

The policy of the College of Physicians and Surgeons of Ontario (CPSO) that regulates FCOI relationships between physicians and the pharmaceutical industry in Ontario is entitled *Physicians' Relationships with Industry: Practice, Education, and Research* and was adopted in 2014 (College of Physicians and Surgeons of Ontario [CPSO], 2014). This policy was preceded by a 1992 policy, entitled *MDs Relations with Drug Companies* (CPSO, 1992) that was first developed and adopted by the Canadian Medical Association (CMA) (CPSO, 1992). What follows is a comparative analysis of these two policies in order to evaluate the extent to which the 2014 policy, versus the 1992 policy, sets standards for and regulates the interests and behaviours of physicians in Ontario. In the interest of providing adequate context, Table 2.1, below, quotes verbatim the General Principles (CPSO, 1992) and Principles (CPSO, 2014) from the 1992 and 2014 policies, respectively. Following Table 2.1 is a comparative analysis of not only these principles, but also some other key sections of each policy.

TABLE 2.1 SIDE-BY-SIDE COMPARISON OF THE PRINCIPLES OF THE CANADIAN PHYSICIANS AND SURGEONS OF ONTARIO (CPSO) IN THE 1992 AND 2014 POLICIES.

***MDs Relations with Drug Companies* (1992): General Principles** (College of Physicians and Surgeons of Ontario [CPSO], 1992)	***Physicians' Relationships with Industry: Practice, Education, and Research* (2014): Principles** (College of Physicians and Surgeons of Ontario [CPSO], 2014)
1. The primary objective of professional interactions between physicians and the pharmaceutical industry should be the advancement of the health of Canadians rather than the private good of either physicians or industry. 2. The relationship between physicians and industry must always be in keeping with the fundamental ethical principles that govern social interactions in general. 3. The relationship between physicians and industry is constrained further by the CMA's Code of Ethics. 4. The interactions between physicians and industry must always respect the fundamental values of Canadian society insofar as these values do not conflict with the fundamental principles of ethics. 5. The practising physician's primary obligation is toward the patient. Relationships with industry are appropriate only if they do not affect the fiduciary nature of the physician-patient relationship. In particular, physicians should avoid any self-interest in their prescribing practices. 6. In any association between a physician who is not an employee of the pharmaceutical industry and the industry itself, the physician should always maintain professional autonomy, independence and commitment to the scientific method.	1. Maintaining [physicians'] professional autonomy, clinical independence, and integrity; 2. Fulfilling their fiduciary duties by acting in the best interests of their patients; 3. Avoiding or recognizing and appropriately managing conflicts of interest that arise in relation to their professional duties; 4. Being transparent in their interactions with industry, and proactively disclosing the details of those interactions where they may be perceived to influence the physician judgment; 5. Participating in self-regulation of the medical profession by complying with the expectation set out in this policy.

There are considerable differences between the General Principles of the 1992 and the Principles of the 2014 versions of the CPSO policies. A clear difference is that the 1992 policy repeatedly refers to the "primary obligations" of physicians, which is language that is consistent with the literature defining and analyzing conflict of interest relationships between physicians and the pharmaceutical industry. In the 2014 policy, this language is absent not only in the Principles quoted above, but also throughout the remainder of the policy. The removal of this language from the 2014 policy is important to highlight because the absence of discussion about the primary obligations of physicians weakens the way that relationships with industry are presented to, and conceptualized by physicians who are governed by this policy.

Although Principle 2 in the 2014 policy states that physicians ought to "[f]ulfill their fiduciary duties by acting in the best interests of their patients", the 1992 policy more clearly and effectively defines that the "[t]he practising physician's primary obligation is toward the patient", which is also absent from the 2014 policy. In place of statements regarding physicians' primary obligations in their professional roles, the 2014 policy is largely concerned with defining acceptable ways for physicians to engage in relationships with industry. For example, where the 1992 policy states that "…physicians should avoid any self-interest in their prescribing practices", the 2014 policy does not. The term "self-interest" is used, but is never further defined. Nevertheless, the removal of these important statements about physicians' roles when it comes to their patients in the 2014 policy means that physicians may not be held to the standard that was previously enunciated. Physicians should be equipped with the necessary language and ideas to not only define their own

professional roles in medicine, but also be able to successfully identify and mitigate conflict of interest relationships should they arise.

The 1992 policy also includes statements, which are not included in Table 2.1, about physicians' participation in surveillance studies and accepting gifts. Where the 1992 policy states that "[p]hysicians are encouraged to participate only in surveillance studies (i.e., phase IV research studies) that are scientifically appropriate for drugs relevant to the area of practice" (CPSO, 1992), the 2014 policy broadens the acceptable roles of physicians in clinical studies by stating that "[p]hysicians must only participate in research involving human participants, including post-marketing surveillance studies (phase IV clinical research), that has the approval of a research ethics board. This includes research that only involves the use of personal health information (PHI)" (CPSO, 2014). Further, although both policies discuss remuneration, the 1992 policy is marginally more specific in the circumstantial parameters within which it is acceptable for a doctor to accept remuneration. The 1992 policy clearly states that:

> It is ethically acceptable for physicians to receive remuneration for participation in approved surveillance studies only if the participation exceeds their normal practice pattern. This remuneration should not constitute enticement…The amount of remuneration should be approved by the relevant review board, agency, or body mentioned previously (CPSO, 1992).

In contrast, remuneration is mentioned twice in the 2014 policy and in both cases, it is stated that "[r]emuneration must only be accepted if it is at fair market value and commensurate with the services provided" (CPSO, 2014). In both of these cases in the 2014 policy, this remuneration is considered in the context of consultation, advisory boards, or investigator meetings. The 2014 policy mentions nothing about requiring the

amount of remuneration to be approved by a relevant committee and also does not set parameters for when this remuneration is acceptable.

Both policies state that physicians must not accept personal gifts from industry. Expanding on this point, the 1992 policy states that "[p]ractising physicians should not accept a fee or equivalent consideration from pharmaceutical manufacturers or distributors in exchange for seeing them in a promotional or similar capacity" (CPSO, 1992). The 2014 includes a similar statement that "[p]hysicians must not request or accept a fee or equivalent compensation from industry in exchange for seeing industry representatives in a promotional or similar capacity" (CPSO, 2014). A subtle difference in these statements between the two policies is that where the 1992 policy more broadly refers to "pharmaceutical manufacturers or distributors", the 2014 policy refers more narrowly to "industry representatives". Although the semantics here are subtle, the difference between "pharmaceutical manufacturers or distributors" and "industry representatives" is important to note. This is because "pharmaceutical manufacturers or distributors" can include any drug company employee, while "industry representatives" can arguably refer more narrowly to drug company employees such as drug detailers, or drug representatives, and exclude physician or non-physician consultants, practice management consultants, key opinion leaders or thought leaders, clinical investigators seeking physicians' assistance, or industry personnel who are involved in the planning and drafting of publication manuscripts (see Chapter 5).

A favourable addition to the 2014 CPSO policy is that should physicians decide to participate in clinical trials, the trials must be "…registered prior to the enrolment of the first participant in a web-accessible research registry" (CPSO, 2014). The reason that this

provision was not included in the 1992 policy is likely because online publicly-accessible clinical trial registries were not yet developed. Another positive addition to the 2014 policy is the definition of a conflict of interest. The 2014 policy defines COI as:

> A conflict of interest is created any time a reasonable person could perceive that a physician's personal interest or relationship with industry is at odds with the physician's professional responsibilities. It is important to note that a conflict of interest can exist even if the physician is confident that his or her professional judgement is not actually being influenced by the conflicting interest or relationship (CPSO, 2014).

However, we see in this comparative analysis that the omission of important language from other areas of the policy can render it difficult to enforce this definition of conflict of interest relationships.

The 2014 Principles and the remainder of the policy no longer state that physicians' relationships with the pharmaceutical industry are also constrained by the CMA's Code of Ethics. An additional important omission from the 2014 policy that was present in the 1992 policy is that "[m]edical curricula should include formal training that is based on [the 1992] guidelines." The 2014 policy contains nothing regarding the inclusion of any formal or informal conflict of interest training within the medical curricula. Another area of weakness in the 2014 CPSO policy, as compared with the 1992 policy, is CME. The 1992 policy states that "…CME clearly distinguishes between education, training…and product promotion", while the 2014 policy makes no such statement.

Thus, a comparative analysis of the two policies indicates that the 1992 policy provides stronger regulation of conflict of interest relationships between physicians and industry than does the 2014 policy. Although the 1992 policy has its own weaknesses that are not discussed here, the 2014 policy is weaker than the 1992 policy in setting

enforceable standards for physicians' relationships with industry as discussed above. The 1992 policy tended to clearly prohibit or disapprove of relationships with the pharmaceutical industry, while the 2014 policy seems to be more concerned not with strong regulation of these relationships, but with the disclosure of conflict of interest relationships with industry in various scenarios. Despite the CPSO explanation that "…in all situations where a conflict of interest arises in the course of professional duties and activities, physicians should recognize the conflict, ensure that a patient's best interests remain paramount and, where appropriate, disclose the conflict of interest to the patient" (CPSO, n.d.), in general, the 2014 policy is not strong enough for the CPSO or physicians to achieve this goal. The policy fails to define what it means by "where appropriate", leaving this up to both voluntary disclosure and personal interpretation by the respective physician. The 2014 policy seems to provide weaker regulation of conflict of interest relationships between physicians and industry because it appears to be more tolerant of these relationships. Finally, a weakness of both CPSO policies is that they fail to mention any penalties should the policies be breached (CPSO, 1992, 2014).

In order to determine whether any physician has been disciplined for violating the CPSO policy on conflict of interest relationships with industry, I contacted the CPSO with this question. According to a personal communication with the CPSO on 2 September 2015, it is not possible to filter search results for physicians that have been disciplined for violating a specific policy because the committees do not reference specific policies in their decisions. On advice from the CPSO on 2 September 2015, I attempted to locate CPSO decisions pertaining to violating its relations with industry policies from both 1992 and 2014 by searching for the key words "conflict of interest" (14 search results, 2

potentially relevant), “relations with industry” (0 search results), “relationship with industry” (4 search results, 0 potentially relevant), “drug company” (0 search results), “pharmaceutical company” (3 search results, 0 potentially relevant), and “pharmaceutical industry” (7 search results, 0 potentially relevant) in the site search. Out of the two potentially relevant search results from the key term “conflict of interest”, one concerned a physician who “…had a conflict of interest, in that he recommended cosmetic products in which he held a personal commercial interest to his patients” (CPSO, 2013) while the second referred to a physician who “…placed himself in a conflict of interest in that he ordered diagnostic testing for some of his patients, to be performed at his clinic, and failed to disclose his proprietary interest” (CPSO, 2015). To summarize, there has been some focus on these issues, but it appears that the net outcome has been permissive policy development, no mention of penalties for policy violations, and no documented enforcement of the policies.

Unfortunately, the apparent lack of application of the CPSO policies over time to cases of FCOI relationships between physicians and the pharmaceutical industry does not mean that these relationships are absent in Canada, or that these relationships do not have the potential to be harmful. In fact, as we will see in the coming chapters of this dissertation, FCOI relationships between the pharmaceutical industry and physicians in Canada are common, poorly regulated, and have the potential to lead to patient and public health harms. FCOI relationships have the potential to broadly affect physicians’ prescribing choices and patient health outcomes, in addition to threatening the integrity of medical research.

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CHAPTER 3

THEORETICAL FRAMEWORK

FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS IN MEDICINE, THE PHARMACEUTICAL INDUSTRY, AND NEOLIBERAL SCIENCE

3.1 CONTEXT AND ORGANIZATION OF THE CHAPTER

Since the 1980s, global sales of drugs have increased at a rate of over 10 percent per year (Sismondo, 2011). This tremendous growth in a period of just over three decades coincides with changes in the structure of research and the general shift toward the privatization of research globally. These changes have affected the means of production of science, arguably more than most of the public are likely to be aware of (Mirowski, 2011; Sismondo, 2011). The commercialization and commodification of knowledge, the institutions in which knowledge is created, and the manner in which it is disseminated have been shaped not by omnipotent puppetmasters behind the scenes, but by a series of converging circumstances that have inspired a certain perspective on social, political, and economic relations (Mirowski, 2011). These sets of relations are a manifestation of the deregulation of industry and how it functions in the free market. These relations have come to position knowledge and its production in such a way that absolves the knowledge

creators of their academic responsibilities, for example, data transparency and pursuing research that advances the health and well-being of the public, to the public (Mirowski, 2011).

This dissertation does not assume that the pharmaceutical industry, or any industry, for that matter, is comprised of people with ill-will, moral challenges, or who engage in greedy transgressions. This dissertation considers the commercialization and commodification of medical research and financial conflict of interest (FCOI) relationships to be structural phenomena so that they can be analyzed as characteristics of neoliberal science. The participation of physicians in the commercialization of science has served to benefit the process of privatizing medical research and, therefore, these relationships must be analyzed within this context. This chapter explores some of the recent transformations in the way that medical research is conducted in the environment of commercialized and privately managed medical research. In this environment, without FCOI relationships between physicians and the pharmaceutical industry, the commercialization, commodification, and private management of scientific research could not be fully realized. FCOI relationships as normative behaviours in medicine are important characteristics of the transformation in the processes of conducting and disseminating medical research. Therefore, FCOI relationships between physicians and the pharmaceutical industry are the focus of the analyses in the four manuscripts, which are the central focus of this dissertation.

The upcoming sections introduce "neoliberal corporate bias" theory by Courtney Davis and John Abraham (Davis & Abraham, 2013) and Abraham (Abraham, 2007), followed by Philip Mirowski's and Robert Van Horne's (Mirowski & Van Horne, 2005;

Mirowski, 2011) theory of "neoliberal science". These analyses are taken one step further by expanding the analysis from the individual level to the organization of medical scientific research at the institutional level. This institutional-level analysis is accomplished by analyzing some normalized institutional behaviours including FCOI relationships, the roles of contract research organizations (CROs), and the far-reaching consequences of CROs in neoliberal science.

3.2 "NEOLIBERAL CORPORATE BIAS" THEORY AND PHARMACEUTICAL INDUSTRY REGULATION

Neoliberal reforms in developed countries have been favourable for companies within the pharmaceutical industry with several important implications for the national authorities tasked with this regulation. These reforms have rendered Health Canada, the United States (US) Food and Drug Administration (FDA), and the European Medicines Agency (EMA) increasingly financially dependent on the pharmaceutical industry for their operating budgets and allowed the FDA and EMA greater flexibility regarding their consultations with the industries that they regulate (Davis & Abraham, 2013). For example, the adoption of user fees, wherein drug companies that are submitting products for market approval are required to pay the regulator for consideration of their submissions, have resulted in regulatory actions that generally favour pharmaceutical companies in the forms of faster approval times and a greater percentage of positive decisions (Davis & Abraham, 2013; Lexchin, 2006). Additionally, neoliberal reforms have encouraged a reduction in the amount and types of evidence that drug companies are required to collect to demonstrate safety and efficacy of specific drug categories when

submitting their applications to the agencies for market approval. Rationales for these reforms included the argument that the public would benefit from faster access to an increased number of drug innovations and enhanced resources available to regulators. Throughout these reforms, pharmaceutical regulators have retained their legal responsibilities and nominal democratic role in promoting and protecting the public's health, safety, and well-being (Davis & Abraham, 2013).

"Neoliberal corporate bias" theory is comprised of two parts. The first part is "neoliberal theory" and the second part is "corporate bias theory" (Davis & Abraham, 2013). Neoliberal theory explains a trend of government-instigated, pro-industry deregulatory reforms that are thought to be in the best interests of patients and public health on the assumption that pharmaceutical innovations promise therapeutic advances and that these objectives are best achieved through a free market approach with minimum regulation (Davis & Abraham, 2013). Neoliberal reforms have reshaped the interests of governments to be more receptive to, and convergent with, industry's interests. In this position, the state's interests become increasingly aligned with industry to the extent that it has fewer issues which private industry needs to negotiate or bargain about with the state (Abraham, 2007). With a minimalist role, the state possesses fewer resources that are independent of industry, so it becomes more challenging for the state to develop and enforce regulations that deviate from industry's interests. The result is an informal atmosphere of communication and trust between the regulator and the industry that it is supposed to be regulating (Abraham, 2007).

Corporate bias theory posits that some organized interest groups, including private industry, have gained advantageous access to the highest levels of the government and

regulatory agencies (Davis & Abraham, 2013). This privileged access has led to institutional relationships which function as partnerships between the government and interest groups. The organized interest groups use these partnerships to their benefit to influence the regulatory agenda (Davis & Abraham, 2013). Corporate bias theory leaves room for the possibility that a government can be relatively strong and proactive, while still encouraging pro-business deregulation in cooperation with industry (Davis & Abraham, 2013). An effect of these relationships, in practice, is that the regulatory agenda becomes biased in favour of the organized interest groups, regardless of other competing regulatory interests (Davis & Abraham, 2013).

The addition of "neoliberal theory" to "corporate bias theory" illustrates the dominant political and socio-structural frameworks that inform the environments in which regulatory agencies have operated, particularly since 1980 (Abraham, 2007). Increasing participation in neoliberal regulatory ideology does not preclude states from still possessing their own interests (Abraham, 2007). Rather, neoliberal ideology has shaped and reformulated the interests of states to be less independent of industry while, at the same time, the state adopts a minimalist role that is consistent with neoliberalism (Abraham, 2007). This role has caused regulatory agencies to have a financial incentive in attracting drug companies as customers to whom they provide services (Abraham, 2007).

Neoliberal corporate bias theory advocates for the analysis of not only regulators and the regulated, but also the broader political and socio-economic contexts that inform decision-making (Abraham, 1995; Davis & Abraham, 2013). Importantly, this framework does not assume that regulatory agencies simply serve corporate capitalist interests

without question, but, rather, it presumes that governments have some "powers of coercion" when it comes to their ability to engage in negotiations and bargaining with organized interests (Abraham, 1995). Neoliberal corporate bias theory assumes that the state has its own interests, which are primarily concerned with financial management within agencies and drug cost concerns within state-funded health care provision (Abraham, 1995). However, state participation in negotiations and bargaining with industry, for example, extends beyond lobbying and pressure group politics into a relationship of "interest interdependence" that can make possible what Abraham (1995) calls a "private interest government" that allows industries to be regulated through "regulated self-regulation", or "enforced self-regulation" as termed by John Braithwaite (1982). In regulated self-regulation, the state's mandate to protect the public devolves into the responsibility of maintaining private industry clientele (Abraham, 1995). While this may be considered to be largely an extreme of corporatism, regulated self-regulation is especially relevant in the context of neoliberal corporate bias theory and pharmaceutical regulation (Abraham, 1995).

An example of this regulated self-regulation can be seen in practice with regard to Health Canada. Until the adoption of Bill C-17 into Canadian law in 2015, Health Canada could withdraw its Notice of Compliance (authorization to market a product) for a previously approved drug, but if it did not withdraw the NOC it did not have the authority to order any drug company to withdraw its products from the market due to harms. In effect, this lack of regulatory authority required drug companies to regulate the safety of their own products that Health Canada had already approved. Whether Health Canada uses its authority from Bill C-17 to withdraw unsafe drugs from the market remains to be seen,

especially since the regulations for this legislation have not yet been finalized. Until Health Canada decides to effectively use its new authority, the level of regulated self-regulation continues to represent voluntary self-regulation. Braithwaite (1982) recognizes that there are situations in which regulated self-regulation, or enforced self-regulation, may be favourable. For instance, government regulators may be under fiscal strain that prevent government investigators from conducting their investigations. Moreover, in the pharmaceutical industry, corporate investigators or compliance inspectors, are employed by drug companies to investigate instances of corporate crime or wrongdoing (e.g., falsifying clinical trial results) in a compliance division that is independent of other departments (Braithwaite, 1982). These investigators tend to be better trained in a technical capacity that is relevant to the pharmaceutical industry as compared to their government counterparts (Braithwaite, 1982). The most clearly defined contradiction that results from the role that corporate investigators assume is that industry ends up regulating its own practices, a clear situation of conflicting interests if the employer is the company being investigated, or if the investigator's employment is contingent on the company's success.

Alternatively, voluntary self-regulation is essentially the model of regulation by which medical schools, professional medical associations (PMAs), and medical journals operate. These institutions and organizations function outside of the jurisdiction of governments when it comes to their institutional policies on FCOI relationships between physicians and industry, as well as those concerning industry involvement in the development of medical education. Medical schools, PMAs, and medical journals each have their own policies, constitutions, guidelines, or a combination thereof and are,

therefore, responsible for regulating themselves in this regard. Because the medical education provided within, or hosted by, these institutions is not considered to be promotional in nature, the content falls outside of the governmental regulation. Institutional-level policies dictate the standards by which individuals within those institutions plan, develop, and consider collaborations for medical education. Importantly, medical education within these fora provide key opportunities for industry involvement if there are gaps in policies or if policies are non-existent. Abraham (1995) argues that neoliberal corporate bias theory provides a useful methodology for analyzing observations of potential corporate biases in the orientation and positioning of interests in government regulation. This theory is also applicable and useful when analyzing the orientation of interests in policies adopted by medical schools, professional medical associations, and medical journals. In this way, the shape of the analyses in the coming manuscripts is informed by not only neoliberal corporate bias theory, but also scientific norms and practices within the context of neoliberal science.

3.3 SCIENCE AS A SOCIAL FUNCTION AND MERTONIAN NORMS OF SCIENCE

American sociologist Robert Merton's (1910-2003) work is a baseline for the common understanding of how the ideal of scientific norms and practices are supposed to work (Hollander, 2003). Merton is recognized for founding the field of sociology of science. His study of the "ethos of science" in one of his major works, "The Sociology of Science: Theoretical and Empirical Investigations" (Merton, 1973), is foundational to the analysis of the culture of neoliberal science. Merton has argued the structural-functionalist

perspective that scientific research serves a social function, which provides knowledge that is considered to be acceptable by the professional scientific community. The social functions of science, therefore, determine the accepted normative behaviours of medical researchers who conduct this research. This structural-functionalist perspective allows societal norms to be analyzed according to the overarching institutions that not only dictate, but also govern normative behaviours in science. As an institution, the function of science is to provide knowledge. Similarly, the task of the field of sociology, as an institution, is to analyze whether the social structure of science supports this function. In order to determine this, Merton argues that the norms of behaviour guide which behaviours and ethics are accepted in scientific practice. When accepted behaviours are in line with institutional priorities, members of the community who abide by these norms are rewarded, while those who behave in opposition to these priorities are sanctioned (Sismondo, 2003).

Merton (1942) presents four norms of behaviour within the ethos of science that, theoretically, work in tandem to help advance the institutional goal of science, which is the extension of certified knowledge. These four norms are universalism, “communism”, disinterestedness, and organized skepticism. Briefly, universalism calls for objectivity in science and in the content of scientific claims by scientists, where the merit of those claims can be evaluated based on their content and not on the characteristics of the scientists who make the claims (Merton, 1942). Therefore, when the characteristics of an individual scientist are questioned, the norm of universalism is violated. When Merton refers to the second norm, “communism”, he intends it to mean that scientific knowledge ought to be a commonly, rather than privately, owned goods in the public domain. The norm of

disinterestedness means not that scientists are expected to be completely altruistic, but that experts should not abuse their authority at the public's expense. Scientific advancements can be appropriated for interested purposes such as those that are commercializable for sale to the public. This appropriation of science by its creators for public consumption leaves room for the public's susceptibility to new mysticisms expressed in scientific terms (Merton, 1942). Therefore, scientists should disengage their research from their individual interests. Finally, Merton's norm of organized skepticism balances universalism by contending that scientific research should be subject to scrutiny that interrogates science as fact as well as through competing perspectives (Merton, 1942).

Merton's scientific norms are introduced in this chapter as the embodiment of a scientific ideal, not as a golden age of science that had once existed. These norms can be applied in analyses of current medical research practices. For example, Merton's principle of "disinterestedness" provides that science ought to be conducted by researchers who can disengage themselves and their interests from their actions and judgements. Disinterestedness assumes that scientists will report their findings fully, regardless of the interests supported by their results (Sismondo, 2003). The commercialization of the research process, which intensifies as industry increasingly funds clinical research, limits the control that biomedical researchers have over their research, collaborations, and release of their results (Blumenthal, Causino, Campbell, & Seashore Louis, 1996). When manufacturers sponsor their own research, the results have been systematically favourable to the sponsors' products and reported safety and efficacy results tend to be more favourable for the sponsor (Bekelman, Li, & Gross, 2003; Downie & Herder, 2007; Lundh, Sismondo, Lexchin, Busuioc, & Bero, 2012).

Furthermore, when legal cases compel pharmaceutical companies to release internal clinical trial and marketing documents, important results that had been concealed or suppressed have come to light. In effect, concealing and suppressing results biases the knowledge base on the safety and efficacy of drugs, indicating that scientific knowledge continues to be constructed by the entities that are responsible for producing it. A ground-breaking study by Le Noury and colleagues (2015b) reanalyzed the data from Study 329, a SmithKline Beecham funded clinical trial, which compared the efficacy and safety of paroxetine and imipramine. Le Noury and colleagues (2015b) recovered approximately 77,000 pages of case report forms (CRFs), which had been kept confidential by SmithKline Beecham, now GlaxoSmithKline (GSK). In Table 3 of Appendix C, Le Noury and colleagues (2015a) revealed that SmithKline Beecham's Study 329 coded serious adverse events (SAEs) in such a way that minimized the appearance of harm experienced by trial participants. In this Table, Le Noury and colleagues (2015a) de-code and re-code the SAEs and, in doing so, exposed SmithKline Beecham's coding of cases in which participants were considered to exhibit suicidal and self-injurious behaviours as "emotional lability". Assigning this euphemistic category to obviously alarming participant experiences was clearly an effort to construct the knowledge base in order to conceal harm while protecting the company's product.

Additional examples of efforts to construct the disseminated knowledge in a way that is favourable to industry sponsors are available in the Drug Industry Document Archive (DIDA) and Truth Tobacco Industry Documents (TTID) online databases. The DIDA and TTID databases were created after lawsuits, and are housed, by the University of California San Francisco (UCSF). Release of internal pharmaceutical industry

documents, now accessible via DIDA, has demonstrated illegal pharmaceutical company advertising and marketing practices, as well as unethical conduct by these industries, academic journals, physicians at academic institutions, and medical education communication companies (MECCs) that pose considerable risks to public health (University of California San Francisco [UCSF], 2015a). Similarly, TTID contains internal tobacco industry documents on advertising, manufacturing, marketing, scientific research, and political endeavours by tobacco companies to promote their products (University of California San Francisco [UCSF], 2015c). DIDA now contains over 3,800 internal pharmaceutical industry documents, and TTID contains over 14 million internal tobacco industry documents that implicate both industries in using unethical means to achieve profit at the expense of public health (University of California San Francisco [UCSF], 2015b). The presence of these archives and the internal industry documents within them illustrate that efforts to construct the disseminated knowledge base are not isolated to the pharmaceutical industry (White & Bero, 2010). While these databases are highly likely to be incomplete, the sheer number of documents that are already housed in these archives illustrate the pervasiveness and insidiousness of the profit motive affecting virtually every step of publishing scientific research, promoting companies' products, and ensuring that these products have favourable reputations among both the academic and public communities. Applied here, Merton's principle of disinterestedness as a baseline of common assumptions about how science operates shows how far the actual behaviours have deviated from those common assumptions.

Another of Merton's principles that serves as a baseline of common assumptions about how science operates in the realm of biomedical research is that of communism, the

notion that scientific knowledge is communal knowledge that is commonly owned. Merton assumes that because scientific knowledge is the most important result of scientific research, the reward must be the publicly owned results. According to Merton, in order to promote the goals of science while still reflecting its assumed traditional social role, the originators of knowledge can claim recognition for their work and creativity without owning or dictating how or by whom those ideas are to be used (Sismondo, 2003). Moreover, Merton has argued that these norms dictate that the results from scientific research should be publicized as widely and as early as possible so that the public can have access to the results and researchers can access more findings than they could have created on their own (Sismondo, 2003).

Merton's conception of these norms present an idealized characterization of science and knowledge dissemination. Instead, in contrast to Mertonian norms, normative behaviours in science in reality may be amenable to secrecy, interestedness, and credulity (Sismondo, 2003). Secrecy may be valued by researchers, especially since science is increasingly competitive and is often associated with financial stakes. Furthermore, with the push to publish, researchers want to ensure that their ideas, methods, and results are not used prior to their publishing them. Across academia and particularly within scientific disciplines, the "publish or perish" ideology of producing knowledge cultivates an environment in which it is believed that although "[t]o state that those who don't publish may as well not do the work in the first place is undeniably harsh, [it is] not unreasonable: if you don't publish, you're wasting everyone's time and taking much-needed funding away from other scientists" (Clapham, 2005). Behavioural norms in science, wherein, scientists act to pursue their own research and funding interests are propagated through

value systems that prioritize the ownership of data, rather than sharing data. These institutionalized value systems legitimize these behaviours and dictate the professional conduct of researchers. Still, Mertonian principles of disinterestedness and communal ownership of research continue to inform our expectation that scientific research results should under no circumstances be suppressed, hidden, or otherwise manipulated (Sismondo, 2003). These popularly understood concepts are, by contrast, playing out in the selective publication, suppression, hiding, and manipulation of clinical trial data (Fugh-Berman, 2013; Goldacre, 2013; Healy, Mangin, & Antonuccio, 2013; Le Noury et al., 2015b; Lexchin, 2005; Melander, Ahlqvist-Rastad, Meijer, & Beermann, 2003; Schott et al., 2010).

3.4 ACADEMIC RESEARCH INSTITUTIONS AND THE KNOWLEDGE-BASED ECONOMY

The pharmaceutical industry benefits from the research, knowledge, and technology developed at academic research universities (Etzkowtiz, Webster, & Healey, 1998). Academic research institutions possess the capacities and abilities to successfully produce research and results, which have been translated into practical commercializable products by interested political and economic actors, including government and industry (Etzkowtiz et al., 1998). Both governments and industrial actors have encouraged the development and sustainability of academic-industrial linkages and partnerships. This sustainability is both motivated and facilitated by governmental institutional and industrial policies and initiatives that promote cooperative academic-industrial partnerships (Etzkowtiz et al., 1998).

By the 1980s, academic-industrial partnerships had become widely considered to be normative relationships between academic researchers and companies in their research fields (Etzkowtiz et al., 1998). In the 1980s, in parallel with increasingly economic and political neoliberal ideology, there was a dramatic rise in formalized university-industry financial relationships (Blumenthal, Gluck, Seashore Louis, Stoto, & Wise, 1986). These linkages were considered to be factors that supported economic growth and sources of new knowledge-flows between universities and industry (Etzkowtiz et al., 1998). Since the 1980s, academic-industrial relationships have become increasingly important for both biomedical science departments at universities and the pharmaceutical industry (Blumenthal et al., 1986). Universities are gradually adopting policies that are aimed at developing favourable economic outputs by campus-based researchers, as well as the involvement of these researchers in knowledge production outside of the university (Etzkowtiz et al., 1998). Academic-industrial partnerships have become considered to be normative relationships, which are often justified on the basis that they foster opportunity for increased funding from not only government policy initiatives, but also lateral ties with private industry that encourage institutionally-driven systems of innovation (Etzkowtiz et al., 1998). A direct result of increased industry support for academic operations within universities has been that the sponsoring industries have adopted prominent roles in universities, which have led to an increased focus on university-based research and innovations that are commercialized for industrial profit, rather than used to further academic interest or the public good (Kenney, 1986; Krimsky, 2004).

Academic research institutions figure prominently in the knowledge-based economy (KBE) in the global arena as a partner to industry. The entrance of universities

into the KBE was motivated by their partnerships with industry. These partnerships have encouraged universities to engage in market-oriented profit-seeking initiatives by securing ownership over the knowledge produced by researchers within the university. In this environment, commercializable and publishable knowledge have become important tradeable commodities. According to Sheldon Krimsky (2004), "…the successful scientist today is the person who can make contributions to the advancement of knowledge while concomitantly participating in the conversion of the new knowledge into marketable products". Krimsky (2004) argues that the transformation of universities into increasingly commercially-driven institutions within the new ethos of commercialism is likely to have pernicious effects.

According to Krimsky (2004), the new philosophy of science within the context of academic commercialism is largely viewed by universities as a favourable trade-off of values. For example, universities consider conflict of interest (COI) relationships that are formed between university faculty and industry to be "…manageable and impossible to eliminate" (Krimsky, 2004). Krimsky's (2004) position is that the commercial exploitation of university-originated knowledge transforms the nature of the traditional university into a commercially-driven knowledge-producing enterprise. A central consequence of this transformation is in the social role of universities. Krimsky (2004) compares the potential for knowledge production within the university to unrealized natural resources from the earth. In this sense, the potential for producing unrealized knowledge in universities is valuable to recognize as a source of knowledge that can be privately exploited. Rather, the assumed role of universities is that they provide environments in which academics who are committed to speaking truth to power can conduct their work on behalf of the public

good and the improvement of society. When efforts are made to restore the traditional values of academic science in the context of business interests, universities tend to become hybrid institutions and suffer the loss of their assumed traditional roles, affecting the social and professional interactions that are considered to be acceptable for medical researchers (Krimsky, 2004).

The increased privatization of university-based research has important consequences for publicly-supported not-for-profit research. Faculty and students are chosen based on the basis of their abilities to realize commercial goals because fewer opportunities exist for public-interest science, encouraging FCOI relationships beginning during students' training and continuing throughout their professional careers (Krimsky, 2004). Public policies and legal decisions are developed with, and informed by, new incentives for universities, faculty, and not-for-profit research institutes. These institutions encourage the commercialization of scientific and medical research through the creation and maintenance of networks and partnerships with for-profit firms (Krimsky, 2004). These liaisons between private industry and academic institutions have resulted in secrecy replacing openness, the privatization of knowledge replacing communitarian values, and the commodification of discovery replacing the notion that university-based knowledge is a good that is free within the social commons (Caffentzis, 2004; Krimsky, 2004). This value has also been threatened by corporate outsourcing of the research that the public largely, still, believes is conducted in the public sector by disinterested university-based researchers.

Mass scale corporate outsourcing of scientific research to private firms has been motivated by factors related to the globalization of corporate research and development

(R&D) in the modern neoliberal regime of knowledge production (Mirowski, 2011). Access to lower-wage research labour that is external to universities allows corporations to disengage themselves from any obligations to academic freedom and ethics, and from providing continuing financial support for local universities or academic research centres. This withdrawal of funding has helped to justify the shift toward outsourcing of R&D in North America, China, India, Brazil, and the Czech Republic (Mirowski, 2011). Although multinational corporations in relatively smaller countries, including the Netherlands and Switzerland, have regularly internationally outsourced their R&D work, since 1980 there has been a sharp increase in the international outsourcing of R&D to low-cost research firms across the pharmaceutical, electrical machinery, computer software, and telecommunications sectors (Mirowski, 2011). This outsourcing is a part of the larger story of modifying and transforming the social, political, and economic roles of the modern corporation (Mirowski, 2011). The following section provides an example of this transformation of the social, political, and economic relations of scientific research and the roles of medical researchers through the creation of the CRO.

3.5 FROM THEORY TO PRACTICE: THE CONTRACT RESEARCH ORGANIZATION

3.5.1 Pharmaceutical research in the contract research organization

The changing landscape of science since the 1980s from one of largely publicly funded research for the public interest to one of privatized and commercialized science further reinforces the necessity for effective medical school, medical association, and

journal policies that prioritize the public's interest in a scientific process that neither conceals bias, nor masks the undue influence of commercial firms on data transparency and results reporting. This is not to assume that scientific research has ever been disinterested, as all research is driven at least in part by social, economic, and political factors, but when research is conducted by and for a for-profit industry, those conducting the research are beholden to the interests of their sponsors at the expense of the public. Two indicators that the scientific process is undergoing transformation and that are directly related to the research that is published in peer-reviewed medical journals include the rise and dominance of the CRO as well as changing conceptions of what it means to hold authorship in a published medical study (Mirowski & Van Horne, 2005).

Pharmaceutical research, including clinical trials, has been largely displaced from the university into purposefully-built, for-profit institutions. Prior to 1990, more than 80 percent of pharmaceutical research was conducted by researchers at academic medical centres (AMCs); however, by 2005, this number was drastically reduced to 25 percent leaving 75 percent of all pharmaceutical research being conducted by for-profit companies (Fisher, 2008). One such type of company that has been responsible for conducting and managing clinical trials and, sometimes, data collection and analysis is called the contract research organization (Fisher, 2008).

CROs are for-profit enterprises whose business goals run in parallel with the firms that pay them (Mirowski & Van Horne, 2005; Mirowski, 2011). They were generally nonexistent prior to 1980 (Mirowski, 2011) and now dominate drug development and clinical trial management in the pharmaceutical sector and are displacing biopharmaceutical and scientific research centres at AMCs (Mirowski & Van Horne,

2005; Mirowski, 2011). CROs are a paradigm of the privatization and commercialization of science and are just one indicator that clinical pharmaceutical research in both corporate and academic settings has shifted to suit the needs of sponsoring firms. This is particularly important as CROs are expanding into nearly every stage of early pharmaceutical research, discovery, development, all stages of clinical trials and their management, dosage formulation and pharmacy services, product branding and marketing, and liaising with the sponsoring company throughout all stages of the regulatory process (Mirowski & Van Horne, 2005; Mirowski, 2011).

The CRO has not operated in isolation of other trends toward privatization such as global expansion of intellectual property and harmonization of regulation, but it has been able to convert research protocols that had been constructed around the initiatives of individual scientists and the medical community into a set of protocols that are geared toward the initiative of controlling the R&D cycles of drugs (Mirowski & Van Horne, 2005). Mirowski and Van Horne (2005) propose that the scientific process and the structures in which scientific research is conducted have been transformed alongside larger political and economic trends toward the privatization of science (Mirowski & Van Horne, 2005).

When scientific research becomes successfully privatized, the boundary between scientific research and marketing is blurred to the point at which they are indistinguishable. It becomes impossible to identify the difference between public relations (PR) spin and scientific research results (Mirowski & Van Horne, 2005; Mirowski, 2011). The inability to identify scientific research from PR spin and marketing is the essence of the "marketplace of ideas" (Mirowski, 2011). CROs and the FCOI

relationships that they foster, help this marketplace of ideas to be realized. Mirowski and Van Horne (2005) argue that this shift to privatized clinical trial management, publishing, displacement of clinical research, and the dominant role of CROs in the scientific process should be viewed, together, as structural changes in the organization of science and serve as an indication of the future directions of privatized science. Importantly, although the development and popularity of CROs have significantly contributed to the profound alteration of the scientific process, these firms have not functioned within a vacuum. Current critiques have, and continue to have to, grapple with the consolidation of trial and information production within CROs, but there were earlier critiques and accounts of industry secrecy. For example, in the 1970s and 1980s, critical voices including scholars, research groups, and activist groups were writing about corporate crime, secrecy, patriarchy, and wrongdoings (Boston Women's Health Collective, 1970; Gazit, 2003). In 1984, Joel Lexchin (1984) published *The Real Pushers: A Critical Analysis of the Canadian Drug Industry* and in the same year, Braithwaite (1984) published *Corporate Crime in the Pharmaceutical Industry*. These works alerted the public to the brewing problem of corporate influence.

The neoliberal environment in which CROs have become established since the 1980s has been conducive to the widespread expansion of the boundaries of intellectual property rights, international motivation for regulatory harmonization, and the subordination of biomedical science to be responsive to global initiatives by private industry (Mirowski & Van Horne, 2005). It is within this environment, argue Mirowski and Van Horne (2005), that CROs have converted traditional scientific research protocols into those which are better suited to controlling the development cycle of new

pharmaceuticals by adjusting to the rhythms of corporatized science. Therefore, rather than studying the future implications of these changes narrowly on the research products or outputs, we should instead focus our efforts on the how the scientific research process has changed (Mirowski & Van Horne, 2005).

The commercialization of medicines began prior to the advent of the CRO. In fact, the development of medicines for commercial reasons has always been present as can be confirmed by the above critical mobilizations in the 1970s and 1980s, as well as by an extensive archive of drug advertisements that were intended to sell medicines for a profit between the 1800s and 2014 (ProCon.org, 2014). Rather, the CRO has helped to take the commercialization of medical research to a new level (Mirowski, 2011). Rather than restructuring its in-house research resources and capacities, Big Pharma contracted out its clinical research to CROs as free-standing commercial entities. Mirowski (2011) argues that although Big Pharma was passively responding to market signals when it began to outsource its research operations to CROs, the CRO is the manifestation of the neoliberal reconstruction of clinical research.

The growth of the CRO industry has been attributed to its increased efficiency, cost savings (although this is debated by Mirowski and Van Horne (2005)), ability to obtain targeted drug expertise, timely clinical trial completion, and outsourced resources for all clinical trial phases. The full-service nature of CROs has been favourable to pharmaceutical companies in the realm of foreign relations when it comes to regional regulatory differences in a globalized economy and coordination of clinical research globally, especially considering the harmonization of drug standards across major

pharmaceutical markets internationally (Lexchin, 2012; Mirowski & Van Horne, 2005; Veerus, Lexchin, & Hemminki, 2013).

3.5.2 Contract Research Organizations: Leopards in the Temple

Despite their presence for almost four decades, the pervasive role of CROs in nearly every stage of discovery, development, and marketing of pharmaceuticals has received little attention by academics (Mirowski, 2011). Attention must be paid to the role of CROs in medical research because these companies have grown into an industry that provide services ranging from conducting and managing phase I-IV clinical trials to assistance in regulatory affairs with a commitment to "…getting drugs through the regulatory process as quickly as possible" (Brooks, 2006; HarrisWilliams&Co., 2014).

The considerable growth in the presence of CROs can be illustrated by their market worth and recent revenue. If it is assumed that the first CRO was established in 1980, then we can estimate that by 1992 the CRO market reached US$1 billion and US$7.9 billion globally by 2001 (Mirowski, 2011). Another estimate by Miriam Shuchman in Mirowski (2011) proposes that the CRO market reached US$17.8 billion in 2007, while a projection by CenterWatch estimated that the CRO market would reach US$25.9 billion by 2010. If we consider revenue growth as an indicator of the growth of CROs in the medical market, Mirowski (2011) claims that the combined revenue of the four largest CROs in the US, all of which were founded in the 1980s, grew from US$3,250 million in 2000 to US$5,943 million in 2006, an increase of almost 55 percent in seven years. A 2015 market research report produced by IBISWorld, estimates that US CROs have a revenue of US$17 billion

and employ 46,738 people in 3,118 companies (IBISWorld, 2015). Outsourcing-Pharma.com estimates that the CRO industry was worth US$27 billion in 2014 and is expected to reach US$45.2 billion by 2022 (Fassbender, 2016).

Mirowski (2011) suggests that an additional method by which the growth of the CRO sector can be assessed is the pharmaceutical industry's budget for R&D that goes to CROs as compared to their budget for R&D conducted at academic health centres. Between 1988 and 1998, the industry's budget for R&D at academic health centres dropped from 80 percent to 40 percent of the total amount spent. Similarly, between 1991 and 2001, this budget dropped from 71 percent to 36 percent (Mirowski, 2011).

Another measure of the growth of CROs is that they are now organized into their own association that represents and advocates for the industry. CROs globally are represented by the Association of Clinical Research Organizations (ACRO), which was founded in 2002 (Association of Clinical Research Organizations [ACRO], 2015). ACRO indicates that it advocates for and represents the world's leading clinical research organizations "…which provide specialized services integral to the development of drugs, biologics and medical devices" (2015). According to ACRO, its members "[c]onduct thousands of clinical trials in more than 140 countries while ensuring the safety of nearly 2 million research participants" (ACRO, 2015). These estimates all indicate that the CRO sector is a central player in the global knowledge economy and has grown to the extent that it has displaced much of the clinical work done in universities and academic hospitals.

Although the reasons for the development of the CRO are not the centre of the discussion here, it is worth mentioning that CROs were an institutional response to the increasingly formalized and ritualized process of pharmaceutical R&D in the United States

after World War II (Mirowski, 2011). Independent of CROs, the regulations imposed by the FDA became more demanding and the pharmaceutical industry considered these new regulations to be extremely onerous. The necessity to recruit subjects, manage them in diverse trials and settings, monitor and record data, analyze the data, and write the results for publication proved to absorb drug companies' time and money, which diverted their potential profits to FDA trials and procedures (Mirowski, 2011). Furthermore, industry felt that in the fast-paced, privatized global economy, academic scientists and drug reviewers were "…largely devoid of deadline pressure" and became considered "[d]ilatory and dawdling scientists" who stalled neoliberal reform (Mirowski, 2011). Despite reduced review and approval times for new drug applications (NDAs), increasingly automated research techniques that allow the screening of hundreds of compounds resulted in a tidal wave of compounds being submitted to the FDA for approval. This tidal wave of NDAs caused additional delays in the review and approval times. For example, between 1990 and 2000, the number of phase I clinical trials in the US increased from 386 to 1,512, respectively (Mirowski & Van Horne, 2005).

Industry believed that the solution to these delays was the corporate scientific researcher, who was accustomed to working with not only deadlines, but also the fine details of the FDA guidelines, rather than complicated patient complaints. These corporate scientific researchers were also favourable to their employers because they understood the importance of narrow research questions, cost-containment methods, and science that was interested in the product, rather than with academic advancement (Mirowski, 2011). According to Mirowski, it was not the advancement of medical knowledge that required more FDA resources, but the amount of data and information that could now be produced

by teams of corporate scientific researchers. In response to industry's desire for a type of research institution that was specifically engineered to its needs, the CRO was developed and drug companies began to outsource their clinical work to these institutions (Mirowski, 2011). Industry has justified, and continues to justify, the outsourcing of clinical research to CROs by arguing that they solve corporate financial problems and allow companies to develop beneficial networks with external companies that can provide clinical trial resources; however, industry tends to ignore important issues such as redefining the research process according to neoliberal objectives, the changing and profit-centred nature of research questions, and the consequences of globalization (Mirowski, 2011). Each of these manifestations of neoliberal science reaffirms the primary objectives of private profit, increased efficiency, and cost savings interests of these institutions.

3.5.3 Normative Practices Associated with Contract Research Organizations

Contract research organizations have imposed a new set of normative behaviours that are suited to controlling the R&D and marketing cycles of new medicines, rather than providing scientists and the medical community with the opportunity to construct research protocols for their research. CROs have constructed normative research practices that are suited to the cadence of corporate privatized science in the global knowledge economy. Some research practices that have become normative in CROs include maintaining data secrecy and confidentiality, avoiding extended treatment regimens that are inconvenient and costly and are irrelevant to the research program, minimizing patient interaction, and amending research protocols to achieve a favourable bottom line (Mirowski, 2011). These

practices can be, undoubtedly, detrimental to the health of the patients who are ultimately treated based on the results of research conducted in this manner.

Although clinical trial recruitment and ethical treatment of participants are not within the scope of this dissertation, it is important to mention that the ability of CROs to recruit patients internationally has cultivated continued debate about the ethical treatment of research participants. While trials conducted and managed by CROs in both developed and developing countries may foster increased access to medicines, the recruitment of subjects from third world countries into clinical trials parallels vulnerability and poverty status (Angell, 1997; Petryna, 2007). The nefarious and unethical treatment of North American clinical trial participants recruited to participate in trials conducted and managed by CROs have also been documented (DrugWatch, 2015; Elliott, 2010, 2011, 2012, 2014). The terms "guinea pigs" and "foreign bodies for sale" have been used to refer to the manner in which the recruitment of international clinical trial participants by CROs is considered within neoliberal science (Elliott, 2010; Mirowski, 2011).

There is limited access to trial data for academic scientific researchers, who are often physicians, are recruited to sign on to the publication of the research to afford it scientific credibility. The credibility of the physicians who are named as authors on these research publications disguises the fact that the authors were unlikely to have had full access to all of the data at each, or any, stage of the clinical and analytic processes (Moffatt & Elliott, 2007; Ross, Hill, Egilman, & Krumholz, 2008; Sismondo, 2007). A selling point of the CRO is that it accommodates private industry's goals by only releasing data if and when the sponsors sanction its release (Mirowski, 2011). If a sponsor does not sanction the release of its data, then the CRO will keep it confidential through a series of restraint

clauses, confidentiality provisions, publication embargoes, and other legal methods to control proprietary information (Mirowski, 2011). Pharmaceutical companies have willingly utilized their legal powers to prevent or restrict disclosure. The CRO assists in these methods of restricting disclosure of almost all aspects of the clinical trial process in which the CRO plays a role (Mirowski, 2011).

Mirowski (2011) explains that some commentators have put forward the counterargument, that when clinical trials are distributed across several clinicians at various geographically located sites, it is highly unlikely that the many small decisions made by clinicians and physicians could favourably bias the results for the sponsor; however, while these sorts of decisions have always affected clinical trials, the privatization of science has insulated these decisions from both internal and external critique. Overall, the result is that the published and otherwise disseminated science is only that which has been agreed to be released by the funder (Bekelman et al., 2003; Friedberg, Saffran, Stinson, Nelson, & Bennett, 1999; Lexchin, Bero, Djulbegovic, & Clark, 2003; Lundh et al., 2012; Mirowski, 2011; Rochon et al., 1994; Sismondo, 2008; Stelfox, Chua, O'Rourke, & Detsky, 1998). CROs also sidestep any issues pertaining to academic freedom because they only answer to the drug companies that hire them and hold no responsibility or accountability for the accuracy of the research results (Mirowski, 2011). For example, CRO employees are not liable for product negligence for a number of reasons including that they are anonymous in the process, there is no single person or small number of people who stand firmly behind the research that they produce, and because the rate of turnover at CROs is high, employees seldom see a project through to its completion (Mirowski & Van Horne, 2005).

This responsibility to only the drug company with which CROs have contracts further insulates the work output at CROs, which is of considerable concern, especially since CROs have gradually become responsible for clinical drug testing (Mirowski, 2011). Furthermore, it is in their contracts with drug companies that CROs will not patent any of the research tools that arise from their contracted research that has been conducted by CRO employees. Because they are, by nature, uncurious, it is the job of CROs to only provide their sponsors with predefined data and they neither receive credit for, nor contribute to, the research that comprises the body of knowledge. If employees in CROs do not comply with their roles, their employment is terminated (Mirowski, 2011). With this transformation from open science to private science, i.e., from academic centres to CROs, universities and academic research centres have become unable to maintain their mandate of science for the public good (Mirowski, 2011) to the detriment of not only the universities as publicly-oriented academic research institutions, but also the scientific research that is published in medical journals and otherwise disseminated.

3.6 THE CHANGING NATURE OF THE "SCIENTIFIC AUTHOR" IN NEOLIBERAL SCIENCE

The CRO is detrimental to the unbiased publication of science in peer-reviewed medical journals. Contrary to popular belief, we cannot consider the body of scientific results that is published in medical journals to be new, comprehensive, and objective information (Mirowski, 2011). Just as scientific research in private industry cannot be disinterested, nor can the publication of results in medical journals. In this private world of science, publishing scientific research in medical journals plays several multifaceted

roles. For example, the journal in which scientific research is published appears to serve as an indication of the significance of the study and that the named authors on the paper benefit from the scientific credit upon its publication (Mirowski, 2011). However, the increasing privatization and commercialization of science have resulted in the questioning of the very role, meaning, and nature of the scientific author. Early in the millennium, a series of high-profile cases of scientific fraud led to questions about who constitutes the designation as a scientific author and whether they are appropriately acknowledged on published papers (Mirowski, 2011). These fraud cases involved reputable authors who revealed that he or she had been inappropriately named as authors on the published papers. The authors argued that they were wrongfully named since they had insufficiently monitored or supervised the protocols of the studies, which were determined to have been "bogus" studies (Mirowski, 2011). These cases led to the re-evaluation of the importance of ghost authorship, where a writing company is hired to craft a manuscript to meet the sponsoring company's needs in how a certain piece of research should be presented. Once the manuscript is ready, one or more researchers or physicians are recruited to sign their names as authors of the study, i.e., as honorary authors, effectively hiding industry's roles in the data analysis and publishing processes (Barbour et al., 2009).

Around the same time as these scientific fraud cases, additional embarrassing cases arose where clinical data that was published in journals differed considerably from the data that was reported to the FDA (Mirowski, 2011). It became evident that stakeholders, other than the named authors, held rights over the publications' texts and data (Mirowski, 2011). Ghost authorship, or the practice in which typically prominent physicians agree to be named on a manuscript that had been created and drafted by unnamed third parties that

possessed final control over the content of the manuscripts, began to be revealed in transcripts from lawsuits against pharmaceutical companies (Mirowski, 2011). Some of these transcripts can be found in the DIDA (UCSF, 2015a). Although ghostwriting occurs across many fields, and certainly before the advent of the CRO, medical ghostwriting differs because it characteristically intends to mislead its readers (Mirowski, 2011).

The pervasive and widespread use of ghostwriting and honorary authorship in pharmaceutical research indicates that the roles of ghostwriters and honorary authors have become normative in medical research internationally (Amsterdam & McHenry, 2012; Barbour et al., 2009; Bosch, Esfandiari, & McHenry, 2012; Bosch, Hernandez, Pericas, & Doti, 2013; Fugh-Berman, 2010; Master, 2012). Medical ghostwriting and, therefore, ghost authorship is ubiquitous across both large-circulation and smaller-circulation biomedical journals, to the extent that ghost journals have also existed. For example, the *Australasian Journal of Bone and Joint Medicine* was one of six fake journals created by Elsevier with the express purpose of publishing articles on behalf of its pharmaceutical company clients (Grant, 2009; Mirowski, 2011). Mirowski assigns a central cause for the prevalence of ghost authorship in the current medical literature to the rise in dominance of CROs in conducting pharmaceutical research (Mirowski, 2011).

Ghost authorship can be viewed as a logical extension of the functionality of CROs. CROs fragment various components of the scientific process, including authorship, which were traditionally performed by academic clinicians or professors of medicine (Mirowski & Van Horne, 2005). CROs are neither interested in, nor pursue academic authorship for their employees. In fact, it would be rare for a CRO employee to expect credit in a publication because of the high personnel turnover and strong control over

intellectual property. Furthermore, doctors, bioinformatics specialists, patient recruitment teams, in-house statisticians, engineers, and other specialists employed by CROs to organize and conduct clinical trials are working for pay and are not interested in receiving authorship (Mirowski & Van Horne, 2005; Mirowski, 2011). Medical ghostwriting characteristically involves physician guest authors, who may be key opinion leaders (KOLs) or thought leaders, terms that describe prominent physicians who are engaged by drug companies to advise on marketing strategies and help boost sales of the companies' products (Moynihan, 2008). Many leading physicians across all specialties and who work in both hospitals and universities are being paid generously to "…peddle influence on behalf of the world's biggest drug companies" (Moynihan, 2008). These roles constitute FCOI relationships. Guest authors who are recruited onto ghostwritten papers and KOLs are used by industry to disguise the embedded corporate interests in order to maintain a façade or smokescreen of independence and mask the FCOI relationships and biases that are created (Moffatt, 2011; Sismondo, 2011).

FCOI relationships are an important method by which corporatized science is legitimated for both public and academic consumption. Furthermore, the commonality of these networks has constructed an environment in which FCOI relationships are considered to be normative behaviours. Sismondo (2003) states that scientific knowledge is the product of the manipulation of local information and that this product can differ in its construction depending on local conditions, including financial interests. Each environment contains tools, such as policies, that can change the ways in which FCOI relationships are regulated, information is considered and, therefore, the ways in which knowledge is constructed and disseminated. Policies can be considered as tools that are

developed, revised, and adopted according to the actors' built networks that have been formed, making policies politically complex documents. Therefore, if we consider changes to the normative scientific process as be one that is structural in nature, as above, then these changes ought to be regulated by policies at the structural level.

The manuscripts that follow this chapter consider FCOI relationships as systemic and structural phenomena. Therefore, these relationships must be regulated at the structural level. Conflict of interest policies at medical schools, professional medical associations, and medical journals are important tools to evaluate the content and stringency of medical education policies in the context of neoliberal corporate bias theory. The theory presented within this chapter has helped to shape the questions that have led to the development of the upcoming manuscripts.

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CHAPTER 4

TOO FEW, TOO WEAK: CONFLICT OF INTEREST POLICIES AT CANADIAN MEDICAL SCHOOLS

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4.1 SUMMARY

Introduction

The education of medical students should be based on the best clinical information available, rather than on commercial interests. Previous research looking at university-wide conflict of interest (COI) policies used in Canadian medical schools has shown very poor regulation. An analysis of COI policies was undertaken to document the current policy environment in all 17 Canadian medical schools.

Methods

A web search was used to initially locate COI policies supplemented by additional information from the deans of each medical school. Strength of policies was rated on a scale of 0 to 2 in 12 categories and also on the presence of enforcement measures. For each school, we report scores for all 12 categories, enforcement measures, and summative scores.

Results

COI policies received summative scores that ranged from 0 to 19, with 0 the lowest possible score obtainable and 24 the maximum. The highest mean scores per category were for disclosure and ghostwriting (0.9) and for gifts and scholarships (0.8).

Discussion

This study provides the first comprehensive evaluation of all 17 Canadian medical school-specific COI policies. Our results suggest that the COI policy environment at Canadian medical schools is generally permissive. Policy development is a dynamic process. We

therefore encourage all Canadian medical schools to develop restrictive COI policies to ensure that their medical students are educated based on the best clinical evidence available, free of industry biases and COI relationships that may influence the future medical thinking and prescribing practices of medical students in Canada once they graduate.

4.2 INTRODUCTION

Conflicts of interest with industry may occur in medical education in the classroom, in the conduct and reporting of research, at the bedside, and in the treatment of patients. The education of medical students should be based on the best clinical information available, unbiased by the commercial interests of industries marketing pharmaceutical or other health products. In many Canadian medical schools, students are taught by faculty who work in partnership with industry, e.g., receive research grants from companies, serve on companies' speakers' bureaus or advisory committees, or own shares in companies (Hébert, MacDonald, Flegel, & Stanbrook, 2010). The financial relationships of faculty with industry may affect, or reasonably appear to affect, the integrity of their academic or publishing interests, professional medical opinions, and the information that they disseminate to medical students (Cho, Shohara, Schissel, & Rennie, 2000; Ehringhaus et al., 2008). These relationships between medical faculty and industry represent conflicts of interest (COI) and compromise not only the public's confidence and trust in medical researchers and universities (Association of American Universities Task Force on Research Accountability, 2001; Cho et al., 2000; Grande, Shea, & Armstrong, 2012), but also the potential for robust, evidence-based clinical education for medical students (Busing, 2008).

When medical school faculty members have ties with, or financial interest in, pharmaceutical companies, they are more likely to report results that are favourable to the sponsoring companies (Cho et al., 2000). Faculty with financial COI tend to publish significantly more, and at a higher rate, than faculty without industry relationships (Zinner, Bolcic-Jankovic, Clarridge, Blumenthal, & Campbell, 2009). At the same time,

these faculty members are also more likely to conduct lower quality, but more commercializable research, as compared with those who undertake independently funded research (Cho et al., 2000; Downie & Herder, 2007). Quality of research is evaluated based on the following criteria: whether clinical trial data is selectively reported, the medication being tested in a trial is compared to one that is known to be inferior, inappropriate doses of a competitor drug are used in a trial, and the length of clinical trials is altered to produce data that is favorable to the sponsors' drugs, among other methods (Cho et al., 2000; Downie & Herder, 2007).

COI relationships are present not only in the classroom, but also surface when industry provides resources to medical schools. Although corporate pharmaceutical funding for education may offer educational opportunities for students, these programs tend to provide students with industry-friendly information, which can compromise clinical judgment if it is at odds with the scientific evidence. For example, between 2002 and 2006, the pain management course for medical and other health science professional students held at University of Toronto was partly funded by grants from Purdue Pharma LP, the maker of OxyContin. As part of the course, a chronic pain management book that was funded and copyrighted by Purdue Pharma was distributed to the students by a lecturer who was external to University of Toronto and had financial ties to Purdue Pharma. Concerns were raised that some of the contents of the book were not consistent with the current best evidence for narcotic medication administration (Ubelacker, 2010). Without effective, stringent COI policies at medical schools to regulate such interactions between faculty, students, and industry, medical students are subject to direct or indirect

interactions with industry, as well as industry resources, that have the potential to influence their future medical thinking and prescribing practices.

The implementation of COI policies has been effective in altering the future prescribing practices of medical residents. Epstein and colleagues (2013) conducted an analysis of the antidepressant prescribing practices of 1652 graduates from 162 psychiatric residency programs in the US before 2001 and after these programs adopted COI policies in 2008. The authors found that residents who graduated before the introduction of COI policies in 2001 tended to prescribe less appropriately than 2008 graduates, where inappropriate prescribing was defined as prescribing heavily marketed and brand reformulated antidepressants (e.g., extended release products) at a higher rate. Furthermore, 2008 residents who graduated from programs with maximally restrictive COI policies prescribed these drugs significantly less often than 2008 graduates from programs with minimally restrictive COI policies.

The Association of Faculties of Medicine of Canada has voted to support the 2008 report by the Association of American Medical Colleges (Association of American Medical Colleges [AAMC], 2008; Busing, 2008) to better manage and, when necessary, prohibit interactions between academics and industry that can create COI and undermine professionalism standards. Previous research on COI policies as applied to Canadian medical schools has shown very poor regulation. Mathieu and colleagues used the American Medical Students Association (AMSA) (2012) scorecard to analyze COI policies at Canadian universities that host medical schools. They found that the university-wide policies were generally weak in the areas of faculty-industry relationships, samples,

sales representatives, on-site and off-site training, industrial relationships, and educating students about COI.

However, the scope of Mathieu and colleagues' study was limited because the authors only analyzed university-wide COI policies and not those specific to medical schools. Further, they omitted the Northern Ontario School of Medicine (NOSM) from their analysis. In addition, they did not contact the universities directly and only relied on institutional policies found via a web search. Finally, only a single coder evaluated the COI policies. To address these limitations, we undertook an analysis of COI policies at both the university and faculty levels to document the current COI policy environment in all 17 Canadian medical schools.

4.3 METHODS

A list of all 17 medical schools (14 English language and 3 French language) in Canada was obtained from the web site of the Association of Faculties of Medicine of Canada (AFMC) <http://www.afmc.ca/faculties-e.php>. The web site of each of the schools was searched in late July 2011 for policies related to COI or documents interpreting policies using the terms "policy", "policies", "conflict-of-interest", "conflicts-of-interest" and "COI" in English, and "politique" and "conflit d'intérêts" in French. The name of each policy and the latest of either the date of adoption or the date of the policy's most recent review were recorded. After a preliminary list of policies for each school was assembled, an e-mail with the list of policies in English or French, as appropriate, was sent to each dean explaining the purpose of the study and requesting

confirmation that this list contained the pertinent policies for the particular medical school. These emails also requested that the deans send us any additional policies we might have overlooked, or draft policies not yet in place. The deans were informed that we were only interested in publicly available policies and while respondents' names would be confidential, the medical schools and their policies would be identified in any subsequent publication. Two reminder emails were sent at one-month intervals. We did not search for, request, or analyze policies from affiliated teaching hospitals.

Policies that were approved as of the end of September 2011 were analyzed. A grading system was modified from those that were already used by AMSA (2012), Chimonas and colleagues (2011), and Mason and Tattersall (2011) for 12 different categories:

- gifts (including meals)
- consulting relationships (excluding scientific research and speaking)
- industry-funded speaking relationships and speakers' bureaus
- honoraria
- ghostwriting
- disclosure
- industry sales representatives
- on-site education activities
- compensation for travel or attendance at off-site lectures and meetings
- industry support for scholarships and funds for trainees
- medical school curriculum (or other documentation of educational objectives and course content)
- samples

AMSA uses a 0 to 3 scoring system where a score of 0 indicates that schools failed to respond to its request to send their policies. Since we initially identified policies using a web search, AMSA's definition of what constituted a score of 0 was not relevant. Both AMSA and Mason and Tattersall regard a permissive policy as equivalent to the absence

of a policy. We graded each category on a scale of 0 to 2, where 0 = no policy or permissive, 1 = moderate, and 2 = restrictive. (See 4.8 Appendix S1 for the detailed scoring criteria for each individual category.) In addition, we scored enforcement measures: is it clear that a party is responsible for general oversight to ensure compliance and is it clear there are sanctions for noncompliance? Each of these enforcement measures was scored either "yes" or "no." We did not attempt to identify if policies had been violated or to grade the severity of sanctions.

Scoring was done by two groups of two people, one for English (AS, KH) and one for French language schools (BM, AJ). Each person independently scored the policies and then compared results within their group. Disagreements were resolved through discussion. Once the scoring was completed, a follow-up e-mail in the appropriate language was sent to each dean. This email included the preliminary scoring for the medical school along with the policies that we used to obtain the score, an explanation of how each area was scored and a request that the dean review the scores for accuracy and notify us if he or she felt that a score was inaccurate. We also requested that the deans send us any new policies developed since the initial contact, but noted that the scores would be based on policies in place as of the end of September 2011. We asked the deans to respond within one month, and if we had not heard from them at that point, two further e-mail reminders were sent at one-month intervals.

After a response from the deans, the scores were reviewed by the original set of scorers, and a final set of scores was derived for each school. Similarly to Chimonas and colleagues (2011), we summed the scores in the first 12 individual categories for each school to come up with a summative score. Each category was weighted equally since

each was identified as vital by a combination of the American Board of Internal Medicine-Institute on Medicine as a Profession (ABIM-IMAP), American Association of Medical Colleges (AAMC), and the Institute of Medicine (IOM) (AMSA, 2012). We view this weighing system as also being applicable to the Canadian situation since the AFMC has endorsed the report by the AAMC on industry funding of medical education (Association of Faculties of Medicine of Canada [AFMC], 2008). For the enforcement categories, the number of "yes" and "no" for each school was summed. We report scores for each category for each school, the summative scores for each school, and the mean for each category.

Since we collected only publicly available information about medical schools' COI policies, the Human Participants Review Committee at York University, which approved this project, waived the requirement for informed consent from the deans of the schools that we contacted.

4.4 RESULTS

Of 17 medical schools contacted, 15 responded to the initial request for policies. Via web searches and responses from deans' offices, we found a total of 50 policies and documents interpreting policies (collectively referred to as policies). Schools had as few as zero (NOSM) and as many as 8 relevant policies (University of British Columbia) per school. In addition, two deans sent us course outlines used in the teaching of COI to medical students. The dates of 16 policies were either not given (9) or were unclear (7). For the other 34 policies, seven were more than 10 years old (one dated back to 1976),

while 12 were passed within two years of September 2011 (Table 4.1). Twenty-one policies were at the medical school level and the remainder (29) were university-wide.

Eleven schools responded when we asked them to review their initial scores, resulting in the revision of scores for five schools that provided policies that we had initially overlooked or that they had not initially sent us. In addition, two schools informed us that they had put in place new policies since our initial survey, while seven were in the process of developing or updating policies.

COI policies received summative scores that ranged from 0 (NOSM) to 19 (Western University, formerly University of Western Ontario), where 0 was the lowest score possible and 24 was the maximum score (Table 4.2). Twelve of the 17 schools scored less than 12/24 (50% of the maximum) and only one scored more than 18/24 (75% of maximum). Cumulative scores of 5 or less reflected ratings of mostly 0 (no policy or permissive) for each category, whereas cumulative scores of 8 or more reflected ratings of 1 or 2 (moderate or restrictive, respectively) for most categories. The highest mean scores were assigned to disclosure and ghostwriting (0.9) and for gifts and scholarships (0.8). Policies on sampling received the lowest average score (0.2), followed by policies on sales representatives (0.3) and speaking and curriculum (0.4). No school had a restrictive policy that applied to samples. Of note, no category received a mean score of 1 or better (Table 4.3). Many COI policies with a rating less than 2 for disclosure failed to require disclosure of both past and present financial ties with industry on a publicly-available website and/or disclosure of any relationships to patients when this relationship may represent a COI.

Fifteen of 17 schools had policies that identified a party responsible for enforcement of the policies (Table 4.2). Examples of responsible parties included "Department Head or equivalent" and "Department Chair, Dean or immediate supervisor."

Eleven of 17 schools had policies that specified sanctions for noncompliance (Table 4.2). An example of such a policy from McGill University contains sanctions ranging from counselling of the individual involved all the way to termination for cause. Ten schools had policies that met requirements for both a specific party responsible for enforcement and specified sanctions for non-compliance.

4.5 DISCUSSION

The 17 Canadian medical schools received scores that ranged from 0 to 19 out of a possible maximum score of 24. The score of 0 was received by NOSM. This low score may reflect, in part, the fact that the school was only established in 2005. Western University received the highest score of 19. Of the 17 medical schools in Canada, over half (10) received summative scores of 5 or less out of 24, indicating that in most of the categories they had either no policy or a permissive policy. No single category managed to achieve an average score of 1 or more.

Fourteen (82%) of the schools received a rating of 0 (no policy or permissive policy) for samples. Samples have been shown to influence medical residents' prescribing practices, with negative implications both for costs and prescribing appropriateness. Adair and Holmgren (2005) have shown that access to drug samples increases the likelihood

that physicians will prescribe heavily advertised and more costly drugs as opposed to cheaper or over-the-counter drugs. We also found that most medical faculties (70%) had permissive policies or no policy concerning faculty involvement in companies' speakers' bureaus. The United States (US) Institute of Medicine's (2009) recent report on COI recommended banning such relationships because speakers' bureaus represent part of a company's promotional activities and the content is often under the company's control (Steinbrook, 2009).

Similarly, 70% of medical faculties had permissive or no policies concerning interactions with sales representatives. Sales representatives have been found to negatively influence prescribing practices, e.g., to lead to more frequent and expensive prescribing and poorer prescribing quality (Spurling et al., 2010). In a comparative study, recently graduated internists who had studied in a program that restricted contact with sales representatives were more critical of the information they provided and saw sales representatives less often than internists from a medical school without such restrictions (McCormick, Tomlinson, Brill-Edwards, & Detsky, 2001). Most schools (70%) also failed to cover conflicts of interest or drug promotion in the curriculum. This gap has important implications for students' abilities to understand the context within which promotional activities occur and to weigh their own responses to ethical challenges that might arise (Austad, Avorn, & Kesselheim, 2011). Finally, nearly all schools had a party responsible for enforcing their policies (15/17) and the majority had sanctions for violations (10/17), but we do not have information on how often these sanctions are applied or how effective they are.

We found that COI policies were most stringent in the areas of disclosure,

ghostwriting, gifts, (considered to be the easiest to prohibit (SCCPD working group on industry relations, n.d.)) and scholarships. These results parallel findings that AMSA obtained in its annual reviews of policies in US medical and osteopathic schools. Its 2012 analysis found that the policy areas that received the highest ratings were those that addressed scholarships, off-campus continuing medical education, purchasing, and gifts (American Medical Student Association [AMSA], 2012). The importance of restricting gifts is emphasized in a review of COI policies at 14 American medical schools that found that exposure to a gift restriction policy during medical school was associated with reduced prescribing of two out of three newly introduced psychotropic medications (King, Essick, Bearman, Cole, & Ross, 2013).

Our findings on ghostwriting are consistent with those of Chimonas and colleagues (2011), even though their rating scale separated out no policy (score = 0) and permissive policies (score = 1). They found that, although existing ghostwriting policies at American medical schools were among the most stringent of all of the policy areas, ghostwriting was also the most neglected policy area. Furthermore, other work has shown that meaningful sanctions for academic fraud are generally absent (Stern & Lemmens, 2011). Because universities reward academic faculty for their publication records, limited enforcement can mean that faculty may find themselves complicit in ghostwriting activities, in spite of policies prohibiting them.

A similar study of Australian medical schools found that their COI policies were even weaker than those at Canadian schools. Eleven out of 15 schools received less than 50% of the maximum possible number of points and only one barely exceeded 66%. All schools either had no policies or had policies that were unlikely to have a substantial effect

on behavior in the areas of on- and off-campus educational activities. Lastly, policies on consulting relationships and disclosure had mean scores below 50% (Mason & Tattersall, 2011).

Our study, in conjunction with the ongoing AMSA survey, the analyses of the US schools by Chimonas and colleagues, and the results from the Australian schools, clearly establishes that the poor control of COI at medical schools is not confined to a single country, but is an issue that needs to be addressed at both national and international levels. One effort to engage medical students in these issues has come from a collaboration between the World Health Organization and Health Action International that has resulted in a manual to teach medical students about pharmaceutical promotion (World Health Organization & Health Action International, 2010). The manual is available in English, French, Russian and Spanish, and has been distributed across a wide range of countries.

This study has some limitations. Two schools did not respond to our initial request for any policies that we might have missed in our web search. Six medical schools failed to review our ratings despite repeat requests; their input could have validated, or alternatively, contradicted our findings. Furthermore, only medical schools' COI policies were within the scope of our study, so we did not consider the policies of affiliated teaching hospitals (e.g., on samples or sales representatives). Hospitals may have had more restrictive policies, but this is unlikely based on previous research (Naylor, 2002).

Policy development is a dynamic process, and some Canadian medical schools have introduced new policies since September 2011, while others continue to revise their policies. It is important for medical schools to continue to develop and improve their COI

policies to mitigate institution-industry relationships and to address the ways in which those relationships may affect the information that is taught to, and the attitudes of, medical students. Policies must also continue to develop, especially since the role of industry within universities continues to evolve (SCCPD working group on industry relations, n.d.).

Practices that were once entrenched into medical culture, including the receipt of gifts, food, and drug samples, in addition to faculty consulting and speaking engagements with industry (Rothman & Chimonas, 2010), should no longer play direct or indirect roles in the education of medical students. Student-industry interactions can influence students' education (Grande, Frosch, Perkins, & Kahn, 2009). Students who have more contact with industry tend to have more favorable attitudes towards these types of interactions (Austad et al., 2011). It has been reported that students who receive gifts from industry feel obliged to rely on industry representatives for information on medications (Industry funding working group, 2011).

More stringent policies are not the only answer for helping to ensure medical education is free from faculty COI, but such policies have been shown to limit the acceptability of promotional items (Grande et al., 2009; Sierles et al., 2005). Medical schools across Canada are encouraged to achieve the most effective and stringent policies to regulate industry relations with both faculty and students.

4.6 ACKNOWLEDGEMENTS

None

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4.8 APPENDIX S1: GRADING SYSTEM FOR CATEGORIES IN POLICIES

1. Gifts (including meals)

2 = All gifts and on-site meals funded by industry are prohibited, regardless of nature or value.

1 = Less stringent limitation on industry-funded gifts (e.g., gifts prohibited above $50/year – or gifts prohibited but meals allowed)

0 = No policy, or policy that would not substantially reduce gifting (e.g., gifts are allowed but discouraged, or limited in a non-specific way to "appropriate," or primarily for the benefit of patients).

2. Consulting relationships (excluding scientific research and speaking)

2 = Consulting relationships with industry must be subjected to institutional review or approval. Additionally, they must either be described in a formal contract, or payment for services must be commensurate to the task.

1 = As above, without the institutional review or approval requirement.

0 = No policy, or policy that would allow consulting relationships to occur without institutional scrutiny or that would allow relationships in which payments are not commensurate with work.

3. Industry-funded speaking relationships/speakers' bureaus

2 = Speaking relationships are prevented from functioning as *de facto* gifts or marketing. An effective policy must not implicitly permit (a) long-term speaking agreements or (b) industry to have a role in determining presentation content. (Some effective policies may explicitly prohibit participation in a speakers' bureau. Other effective policies contain elements such as limits on compensation and reimbursement and a requirement to ensure the scientific integrity of information presented.)

1 = Industry-funded speaking relationships are regulated, but with less stringent limits on longevity, content or compensation.

0 = No policy, or policy that does not define the limits on longevity, content or compensation.

4. Honoraria

2 = No acceptance of honoraria; compensation must be at fair market value and publicly disclosed

1 = Limits on accepting/disclosing honoraria.

0 = No policy, or no limits on acceptance.

5. Ghostwriting

2 = Ghostwriting is not permitted.

1 = Few or no restrictions; management is left to individual discretion.

0 = No policy.

6. Disclosure

2 = Personnel are required to disclose past and present financial ties with industry (e.g., consulting and speaking agreements, research grants) on a publicly-available website and/or disclose such relationships to patients when such a relationship might represent an apparent conflict of interest.

1 = Universally-required, internal disclosure to the medical school or hospital administration. (Policies requiring disclosure only when presenting or publishing do not meet this criterion.)

0 = No policy.

7. Industry Sales Representatives

2 = Pharmaceutical and device representatives are not allowed to meet with faculty regardless of location, or are not permitted to market their products anywhere inside the medical center and associated clinics and offices. (Exceptions may be made for non-marketing purposes, such as training on devices or equipment.)

1 = Pharmaceutical representatives are permitted to meet with faculty, but with significant limitations (e.g., only in non-patient care areas or only by appointment). Exceptions as above.

0 = No policy, or policy that does not substantially limit access.

8. On-site Education Activities

2 = Industry is not permitted to provide direct financial support for educational activities, including Continuing Medical Education (CME), directly or through a subsidiary agency. (However, companies may contribute unrestricted funds to a central fund or oversight body at the academic medical center, which, in turn, would pool and disburse funds for programs that are independent of any industry input or control.)

1 = Less stringent limitations to ensure independence of educational content (e.g., standards to establish freedom from industry influence of content, such as review and approval of presentations; language that prevents industry from selecting the speaker; or language such as: industry funding may be allocated for a particular topic, but must be provided directly to the department, not to individuals).

0 = No policy, or a policy that would not substantially limit industry influence over educational activities (e.g., industry funding must be disclosed).

9. Compensation for Travel or Attendance at Off-site Lectures & Meetings

2 = Personnel may not accept payment, gifts or financial support from industry to attend lectures and meetings. (An exception may be made for modest meals, if part of a larger program.) Travel support may only be accepted if it is subject to institutional approval or industry is prevented from selecting ("earmarking") the recipients. Note: speaking and consulting relationships are evaluated separately in domain 1.

1 = Less stringent limitations.

0 = No policy, or a policy that would not substantially limit participation in industry-funded events and meetings.

10. Industry Support for Scholarships & Funds for Trainees

2 = The policy must either prevent industry from earmarking or awarding funds to support the training of particular individuals (recipients must be chosen by the school or department), or the policy must mandate institutional review of the giving of funds. (This does not preclude grants that fund a specific research project.)

1 = Less stringent limitations.

0 = No policy, or a policy that would not substantially regulate industry funding of scholarships and funds for trainees.

11. Medical school curriculum (or other documentation of educational objectives/course content)

2 = Students are trained to understand institutional conflict-of-interest policies and recognize how industry promotion can influence clinical judgment.

1 = Curriculum addresses conflict of interest in a more limited way (e.g., training on policies only).

0 = No policy (not addressed in curriculum or elsewhere).

12. Samples

2 = Industry samples are prohibited, except under certain narrow circumstances approved by the institution that protects the interests of patients and prevent the use of samples as a marketing tool (e.g., policies that allow samples under limited circumstances with the approval of the Pharmacy and Therapeutics (P&T) Committee or policies that incorporate samples into a larger program designed to ensure the availability of brand-name and generic medications to underinsured patients; if the circumstances of the specific program are not defined, the policy should define the approvals process). Where there is a specific program in place, the policy must prevent samples from being given directly to physicians by pharmaceutical sales representatives. Samples must not be for the personal use by physicians.

1 = Samples or vouchers for medications may be provided, but with significant limitations (e.g., samples may not be given directly to physicians, samples must be dispensed or controlled by pharmacy department).

0 = No policy, or a policy that does not substantially limit the use of samples (e.g., samples limited for formulary items or samples not for personal use.

13. Enforcement

A. Is it clear that there is a party responsible for general oversight to ensure compliance? (Y/N)

B. Is it clear there are sanctions for noncompliance? (Y/N)

TABLE 4.1: POLICIES PER SCHOOL AND DATE OF EACH POLICY

School	Name of policy	Date of adoption/most recent review
Dalhousie University	Guidelines for the relationship between medical education and health related industries (S*)	September 2011
	Policy on conflict of interest (U†)	June 24, 2002
Laval Université	Normes de gestion des Fonds de soutien à l'enseignement des programmes de residence (S)	June 18, 2010
	Politique de la Faculté de médicine sur les relations entre les membres de la Faculté de médecine de l'Université Laval et les entreprises privées relativement aux activités et aux programmes de formation sous la responsabilité de la Faculté (S)	December 19, 2008
	Politique sur l'intégrité en recherché et création et sur les conflits d'intérêts (U)	May 20, 2009
McGill University	Code of conduct: faculty of medicine (S)	No date given
	Handbook: student rights and responsibilities (U)	2010
	Recognizing conflicts (U)	No date given
	Regulations concerning investigation of research misconduct (U)	May 25, 2010
	Regulation on conflict of interest (U)	June 15, 2009
McMaster University	Guidelines regarding management of commercial/private sector/government relationships in research and education (S)	January 23, 2008
	Joint intellectual property policy (U)	May 27, 1998
	Policy on support of continuing education events from commercial sources (S)	2007

	Postgraduate education guidelines for interaction with the pharmaceutical industry (S)	No date given
	Statement on consulting policy and procedures (U)	January 14, 1976
	Statement on conflict of interest in research (U)	March 11, 2009
Memorial University of Newfoundland	Conflict of interest (U)	March 31, 2011
	Integrity in scholarly research (U)	February 12, 2001
	Procedure for investigation reports of misconduct in research (U)	No date given
Northern Ontario School of Medicine	No policies	No policies
Queens University	Physicians and industry – conflicts of interest (S)	Date uncertain
	Policy for disclosure on conflict of interest (S)	August 17, 2001
Université de Montréal	Règlement sur les conflicts d'intérêts (U)	November 24, 2009
Université de Sherbrooke	Guide sur les relations entre les milieux de formation en santé et les entreprises (S)	March 17, 2010
	Politique, règles et proc édures sur l'intérité en recherché et sur les conflicts d'intérêts (U)	May 30, 2006
University of Alberta	Conflict of interest and conflict of commitment reporting and assessment policy (U)	November 16, 2009
	Conflict policy – conflict of interest and commitment and institutional conflict (U)	June 26, 2009
University of British Columbia	Conflict of interest/commitment declaration – steps (U)	Date uncertain
	Conflict of interest and conflict of commitment (S)	November 2007
	Dean's COI/COC review committee (S)	November 7, 2006
	Definitions (U)	Date uncertain
	Duty to disclose (U)	Date uncertain

	Frequently asked questions (FAQs) (U)	Date uncertain
	Managing conflicts – what to do (U)	Date uncertain
	Reviewer resources (U)	Date uncertain
University of Calgary	Conflict of interest policy (U)	September 1, 1987
	Disclosure of potential financial conflict of interest for use by planning committees for continuing medical education and professional development programs (S)	No date given
	Disclosure of potential financial conflict of interest for use by speakers for continuing medical education and professional development programs (S)	No date given
	Research policy for integrity in scholarly activity (S)	December 9, 1992
University of Manitoba	Interactions between the University of Manitoba's Faculty of Medicine and the pharmaceutical, biotech, medical device, and hospital and research equipment and supplies industries ("Industry") (S)	June 3, 2009
	Policy on industry relations (S)	No date given
University of Ottawa	Conflict of interest – members of staff (U)	October 20, 2009
	Interacting with industries and outside agencies in a teaching environment (U)	November 19, 2008
	Interactions between the Faculty of Medicine and the pharmaceutical, biotechnology, medical device, and hospital and research equipment and supplies industries (S)	September 2011
	Standards of ethical and professional behaviour (S)	no date given
University of Saskatchewan	Conflict of interest (U)	December 12, 2008
	Research integrity policy (U)	June 17, 2010

University of Toronto	CEPD policy on support of University of Toronto sponsored continuing education activities from commercial sources (S)	November 15, 2004
	Policy on conflict of interest – academic staff (U)	June 22, 1994
Western University (formerly University of Western Ontario)	Policy and guidelines for interactions between Schulich School of Medicine and Dentistry and pharmaceutical, biotech, medical device and research equipment supplies industry ("Industry") (S)	June 4, 2010
	Recommendations and frequently asked questions (FAQs) (S)	no date given

*S = School-specific policy

†U = University-wide policy

TABLE 4.2: MEDICAL SCHOOLS AND SCORING FOR INDIVIDUAL CATEGORY

School	Strength of policy			Total score (percent of maximum)	Enforcement	
	No policy or permissive	Moderate policy	Restrictive policy		Party responsible for enforcement	Sanctions for violations
	(score = 0)	(score = 1)	(score = 2)		(Yes/No)	(Yes/No)
Western University (formerly University of Western Ontario)	honoraria	curriculum, sales representatives, samples	compensation, consulting, disclosure, ghostwriting, gifts, on-site education, scholarships, speaking	19 (79)	Yes	Yes
University of Manitoba	curriculum, samples	compensation, disclosure, honoraria, sales representatives	consulting, ghostwriting, gifts, on-site education, scholarships, speaking	16 (67)	Yes	Yes
University of Ottawa	consulting	compensation, curriculum, disclosure, on-site education, samples, sales representatives, speaking	ghostwriting, gifts, honoraria, scholarships	15 (63)	Yes	Yes
Dalhousie University	samples, speaking	compensation, consulting, curriculum, disclosure, on-site education, sales representatives	ghostwriting, gifts, honoraria, scholarships	14 (58)	Yes	Yes
Université de Sherbrooke	curriculum, speaking	consulting, disclosure, gifts, honoraria, on-site education, sales	compensation, ghostwriting, scholarships	13 (54)	Yes	Yes

		representatives, samples				
Laval Université	ghostwriting, sales representatives, samples, speaking	consulting, disclosure, gifts, honoraria, on-site education	compensation, curriculum, scholarship	11 (46)	Yes	Yes
University of Toronto	curriculum, ghostwriting, gifts, sales representatives, samples	compensation, disclosure, honoraria, on-site education, sales representatives, samples	consulting	8 (33)	Yes	No
McMaster University	compensation, curriculum, ghostwriting, gifts, sales representatives, samples, scholarships, speaking	consulting, disclosure, honoraria	on-site education	5 (21)	Yes	No
University of British Columbia	compensation, curriculum, ghostwriting, on-site education, sales representatives, samples, scholarships	consulting, disclosure, gifts, honoraria, speaking		5 (21)	Yes	No
McGill University	compensation, consulting, gifts, honoraria, on-site education,	curriculum, disclosure	ghostwriting	4 (17)	Yes	Yes

	sales representatives, samples, scholarships, speaking					
Memorial University of Newfoundland	compensation, curriculum, ghostwriting, honoraria, on-site education, sales representatives, samples, scholarships, speaking	consulting, disclosure, gifts		3 (13)	Yes	Yes
University of Calgary	compensation, consulting, curriculum, gifts, honoraria, on-site education, sales representatives, samples, scholarships, speaking	disclosure	ghostwriting	3 (13)	Yes	No
University of Saskatchewan	compensation, consulting, curriculum, gifts, honoraria, on-site education, sales representatives, samples, scholarships, speaking	disclosure	ghostwriting	3 (13)	Yes	Yes

Université de Montréal	compensation, consulting, curriculum, ghostwriting, honoraria, on-site education, sales representatives, samples, scholarships, speaking	disclosure, gifts		2 (8)	Yes	No
Queens University	compensation, consulting, curriculum, disclosure, ghostwriting, gifts, honoraria, on-site education, sales representatives, samples, speaking	scholarships		1 (4)	No	No
University of Alberta	compensation, consulting, curriculum, ghostwriting, gifts, honoraria, on-site education, sales representatives, samples, scholarships, speaking	disclosure		1 (4)	Yes	Yes
Northern Ontario	compensation,			0 (0)	No	No

School of Medicine	consulting, curriculum, disclosure, ghostwriting, gifts, honoraria, on-site education, sales representatives, samples, scholarships, speaking					

TABLE 4.3: NUMBER (%) OF CANADIAN MEDICAL SCHOOLS WITH POLICIES IN EACH CATEGORY AND STRENGTH OF POLICY

Category	No. of schools (%) with no policy or permissive policy (score = 0)	No. of schools (%) with moderate policy (score = 1)	No. of schools (%)with restrictive policy (score = 2)	Mean score
Ghostwriting	9(53)	0 (0)	8 (47)	0.9
Disclosure	2 (12)	14 (82)	1 (6)	0.9
Gifts	8 (47)	5 (29)	4 (24)	0.8
Scholarships	9 (53)	2 (12)	6 (35)	0.8
Consulting	8 (47)	6 (35)	3 (18)	0.7
On-site education	9(53)	5 (29)	3 (18)	0.6
Compensation	10 (59)	4 (24)	3 (18)	0.6
Honoraria	9 (53)	6 (35)	2 (12)	0.6
Curriculum	12 (70)	4 (24)	1 (6)	0.4
Speaking	12 (70)	3 (18)	2 (12)	0.4
Sales reps	12 (70)	5 (29)	0 (0)	0.3
Samples	14 (82)	3 (18)	0 (0)	0.2

INTEGRATIVE DISCUSSION

Medical education provided by Canadian medical schools is the first formal exposure that medical students in Canada receive to not only treatment and diagnostic information that they will use in practice, but also acceptable and appropriate professional conduct. Canadians rely on physicians and, therefore, on the knowledge and skills that these physicians receive at Canadian medical schools. At medical school, medical students must study and learn important clinical skills, but equally as important to patients is how medical students learn to apply those skills. Canadian medical schools must set an example and impart to their students the importance of not only their critical analysis of medical information, but also seeking out information that has been developed and analyzed independently from commercial industry.

In the study on Canadian medical schools' policies on conflict of interest relationships with the pharmaceutical industry (Chapter 4), we found the policies to be generally weak. The permissiveness of these policies indicate that there is room for industry influence in medical education. The policies were most restrictive in the areas of disclosure, ghostwriting, gifts, and scholarships. The policies were moderately restrictive in the areas of faculty's receipt of honoraria, compensation, industry involvement in on-site education, and participating in consulting relationships. The policies were most permissive in the areas of faculty's receipt of samples, seeing drug company sales representatives, speaking engagements, and curriculum for students on conflict of interest relationships. Permissive policies in these areas provide an opportunity for the industry-originated information that physician-faculty may receive during these interactions to be taught to students. Furthermore, the general lack of requirement for medical schools to

cover conflict of interest relationships and drug promotion in their curricula has important consequences for medical students. Without training on relationships with industry, how to accurately identify these relationships, and what these relationships mean in the context of conducting and interpreting medical research and knowledge, medical students experience a disadvantage early in their careers when it comes to understanding the context within which medical research, education, and promotional activities are conducted and disseminated. This disadvantage is especially important considering the growth of the for-profit drug promotion industry, which has been developed for the purpose of promoting and selling medications.

While the drug promotion industry conducts some of its promotion clearly as advertising, it also works behind-the-scenes of medical research that is published in medical journals. Both medical students and practicing physicians depend on published medical journal articles for clinical information and the best available evidence on which they can base their clinical decisions. Therefore, it is essential that the practices of corporate science are de-coded and critically analyzed. The next manuscript (Chapter 5) examines the role of the drug promotion industry in the medical research, interpretation, and publishing processes within neoliberal science.

CHAPTER 5

HONEST AUTHORSHIP: A GLOSSARY AND ASSESSMENT TOOL TO HELP PREDICT VULNERABILITY TO CORPORATE BIAS IN MANUSCRIPTS SUBMITTED TO MEDICAL JOURNALS

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5.1 SUMMARY

Corporate science and scientific publishing that adheres to neoliberal objectives has encouraged important shifts in the processes by which medical research is conducted and data is collected, interpreted, and published. The literature has documented many strategies that have been used by the pharmaceutical industry and related entities to conceal not only its involvement, but also the biases that its funding brings to various and, in some cases, all levels of research and writing in published clinical research. A literature review led to the development of a glossary and assessment tool. The glossary includes a number of key words and academic interpretations describing practices that have been used by the pharmaceutical industry to meet the needs of commercial science, rather than the public good. The assessment tool provides a method by which researchers and journal editors can identify which manuscript submissions are likely to be vulnerable to bias as a result of industry involvement in the research and publications processes. The tool can be further refined to capture additional practices as the shift to increasingly privatized and commercialized science continues.

KEYWORDS: pharmaceutical industry, promotion, medical journals, corporate science, neoliberal science, financial conflict of interest relationships, authorship disclosure policies, transparency

5.2 INTRODUCTION

Medical research and publishing continues to be increasingly conducted by, or in partnership with, industry (Fisher, 2008; Mirowski, 2011). Medical journals are gatekeepers to, and an important medium for, the dissemination of medical research to physicians, medical researchers, and students. Systematic reviews and meta-analyses, derived from research articles published in peer-reviewed medical journals, are regarded as the highest forms of evidence and are used alongside published clinical trials and supporting articles in clinical decision-making. Traditionally, medical researchers, physicians, and the public expect peer-reviewed medical journals to serve as dissemination and translation tools for critical analyses of evidence-based medicine (EBM); however, some published literature in medical journals has shifted in its use from EBM to marketing-based medicine (MBM). MBM is a term used to describe research results that have undergone a series of refinements that, together, influence medical knowledge and medical practice. Some of these practices include the suppression and spinning of negative data, ghostwriting, and ghost management (Healy, Mangin, & Antonuccio, 2013; Healy, 2012; Sismondo, 2007; Spielmans & Parry, 2010).

The pharmaceutical promotion industry has become a profitable sector in the global economy. This industry is comprised of not only drug companies, but also supporting entities, which provide services such as running and managing clinical trials, collecting and analyzing clinical trial data, drafting manuscripts to be submitted to medical journals, and developing content for continuing medical education (CME) programs (Mirowski & Van Horne, 2005). Together, these firms and entities employ thousands of marketers, writers, and publication managers, who, in the process of developing

manuscripts, medical lectures, commentaries, CME, and other documents aimed at disseminating knowledge to clinicians, shape the discourse around disease states by embedding pro-industry marketing messages that reflect positively on manufacturers' products (Fugh-Berman, Pike McDonald, Bell, Bethards, & Scialli, 2011; Fugh-Berman, 2010).

This paper examines the medical publishing culture as part of the scientific process that increasingly operates according to the norms and values associated with neoliberal science. Neoliberal science refers to a regime of scientific management that commonly entails the rollback of public funding for universities, narrowing of research agendas to focus on commercializable research as defined by commercial funders, commodification and commercialization of knowledge, and an increasing reliance on the market as an indicator of scientific success (Lave, Mirowski, & Randalls, 2010). Dissolution of the scientific author, or the fragmentation of the traditional authorship role into a series of roles adopted by employees within various organizations, has also been associated with neoliberal science (Lave et al., 2010).

One consequence of neoliberal science is that the role of peer-reviewed medical journals has been compromised by the increasingly industry-centric environment in which medical research and writing are conducted. Although medical journals have been increasingly adopting authorship, contributorship, and financial conflict of interest (FCOI) disclosure policies, the utilization of, requirements for, and methods of collecting this information tend to differ by journal (Bosch, Pericas, Hernandez, & Torrents, 2012; Wager, 2007). Medical journals also tend to have substantial variation in their authorship and FCOI disclosure policy requirements (Blum, Freeman, Dart, & Cooper, 2009).

Furthermore, the nature of voluntary policy adoption and enforcement by journals, in addition to the use of "weak definitions or convenient understandings" of scientific publishing roles and responsibilities, has led to industry's exploitation of these policies in order to conceal its involvement in ways that violate the generally expected scientific and medical publishing norms (Matheson, 2011). Therefore, standardizing and understanding the language associated with medical publishing and developing assessment tools to assess medical journal policies is important to encourage uniformity in developing effective and enforceable authorship, FCOI, and data transparency policies.

Internal industry documents from the Drug Industry Document Archive (University of California San Francisco [UCSF], 2015) have provided glimpses into the industry's publishing culture. Within this culture, the pharmaceutical promotion industry uses interpretations of terminology that outmaneuver current authorship and FCOI policies, thereby, concealing its involvement in the medical research, writing, and publishing processes (Matheson, 2011). Therefore, a glossary and assessment tool that standardizes the language around drug companies' behind-the-scenes involvement in publishing may assist medical journal editors and peer-reviewers in their assessments of the content within manuscript submissions.

The following section provides an analysis of the implications of the changing landscape of science from one that traditionally was oriented to expanding scientific knowledge to one that is increasingly dictated by corporate interests. Simultaneously, the practices of clinical research and medical writing have shifted to adhere to the objectives of neoliberal science. This analysis proceeds through introducing a series of normative medical research and writing practices that work in tandem to ensure that the business

goals of sponsors are being met. These analyses are followed by the methodology and findings of this study. First, a glossary provides a modest initial entrance into, and understanding of, the practices of corporate medical publishing. Second, this paper provides a assessment tool that is informed by the glossary with an eye to disclosure and transparency of the roles of research teams and corporate study funders in the research and manuscript development processes.

5.3 THE CHANGING LANDSCAPE OF MEDICAL SCIENCE RESEARCH

Many of the original research and review articles concerning medications that are submitted to and accepted by peer-reviewed medical journals not only originate from, but also are funded by the manufacturers of pharmaceutical treatments that are being evaluated. This institutional conflict of interest relationship, in which drug companies are responsible for conducting their own clinical trials, analyzing and, subsequently, facilitating the publication of their own results, has led to the skewing of the medical literature and knowledge base through practices including ghost management and publication planning (see Fugh-Berman & Dodgson, 2008; Sismondo, 2007, 2009), design bias (see Fries & Krishnan, 2004), suppressing and spinning of negative data (see Aursnes & Klemp Gjertsen, 2008; Le Noury et al., 2015; Lundh, Sismondo, Lexchin, Busuioc, & Bero, 2012; Melander, Ahlqvist-Rastad, Meijer, & Beermann, 2003; Ninan, Poole, & Stiles, 2008; Schott et al., 2010; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008), and medical ghostwriting (see Barbour et al., 2009; Bosch, Esfandiari, & McHenry, 2012; Fugh-Berman, 2010; Gotzsche et al., 2007; Lacasse & Leo, 2010; Leo,

Lacasse, & Cimino, 2011; Logdberg, 2011; McHenry & Jureidini, 2008; Ross, Hill, Egilman, & Krumholz, 2008; Sismondo, 2009). These strategic practices serve to ensure that the medical literature is generally favourable to industry sponsors' products and, in the process, traditional science and medical journals have been captured by the pharmaceutical industry and strategically used to increase profits for the sponsoring drug companies.

Scientific research and management have shifted dramatically since the 1980s with the increasing adoption of neoliberal policies and regulations globally (Lave et al., 2010). In the 1980s, critical scholars were questioning, observing, and analyzing the effects of private industry on pharmaceutical research and efforts to advertise their products. For instance, in 1984, Drs. Joel Lexchin (1984) and John Braithwaite (1984) separately published trailblazing books aptly titled *The Real Pushers: A Critical Analysis of the Canadian Drug Industry* and *Corporate Crime in the Pharmaceutical Industry*, respectively. Since then, academics across scholarly disciplines have undertaken research that critically analyzes the ways in which medical research and its management have been increasingly determined and dictated by neoliberal policies that prioritize private profit over the public's right to access information and unbiased healthcare. Neoliberal science has, and continues to have, difficult to ignore consequences for the organization, practice, and social implications of science (Lave et al., 2010).

5.3.1 Contract research organizations, medical writing organizations, and medical communications companies

Corporate scientific research within the pharmaceutical industry has grown through university-industry linkages and contracts with supporting entities, including contract research organizations (CROs), medical writing organizations (MWOs), and medical communications companies (MCCs) which have transformed the way that pharmaceutical research is conducted and communicated (Mirowski & Van Horne, 2005). MWOs and MCCs may be contracted by drug companies to write and prepare manuscripts for submission to medical journals and provide "near complete drafts of review manuscripts to authors for editing, in addition to managing submissions and revisions" (Cosgrove, Vannoy, Mintzes, & Shaughnessy, 2016; Ross et al., 2008). CROs have grown to become full-service firms that offer a range of services "…from initial screening of molecules for biocompatibility, in vitro screening, pharmacokinetic modeling, chemical synthesis and analysis, all phases of clinical testing, dosage formulation and pharmacy services, to all aspects of the regulatory process" (Mirowski & Van Horne, 2005). CROs, MWOs, and MCCs represent a manifestation of the privatization of science and the scientific process in the contemporary clinical pharmaceutical research laboratory within academic and corporate locales.

Since the 1980s, CROs have grown from small specialized boutique firms that offered pharmaceutical companies the opportunity to outsource a limited set of services into an industry that has expanded its role into almost every stage of pharmaceutical research and development (R&D), discovery, pre-clinical and clinical trial research and management, and marketing phases of drug companies' products (Mirowski & Van

Horne, 2005). The dominant role of CROs can be illustrated by their revenue growth from US$1.0 billion to US$7.9 billion between 1992 and 2001 and the growth in the number of clinical trial participants they oversee from 7 to 20 million, many of whom are located outside North America, in Asia and Eastern Europe (Sismondo, 2008). Also during this time, drug companies redirected approximately half of their financial support for clinical trials out of academic research centres and into CROs (Sismondo, 2008). This shift in funding from academic institutions to the private sector has been accompanied by a shift in research protocols that prioritize private control over the R&D cycle, predicated on the interests of increasing the efficiency and speed of clinical trial research and analysis in corporate science (Mirowski & Van Horne, 2005).

CROs manage various scientific protocols to meet the goals of their contracts with drug companies. This commercial-oriented management has led to consequences for informed consent, restrictions on disclosure of research results through combinations of restraint clauses, confidentiality provisions, publication embargoes, legal controls over information that is defined by the sponsoring company as commercially confidential information (CCI) or proprietary information, and the ethical treatment of clinical trial participants in poor and developing regions globally to the point that these participants have been termed “foreign bodies for sale” (Mirowski & Van Horne, 2005, p. 232). Importantly, because academic research centres have been unable to compete with CROs, they have endeavoured to increase their clinical research services in an effort to regain the contracts that they lost to CROs (Campbell, Weissman, Moy, & Blumenthal, 2001; Mirowski & Van Horne, 2005).

Of principal concern to CROs is the delivery of a research product within deadline and under budget. Characteristically, relationships between CROs and drug companies with which they have contracts are dictated by and subordinate to the objectives of the sponsor. Furthermore, the "'sweatshop' character of the work conducted in CROs" (Mirowski, 2011) adds another layer of practices that contribute to the undermining of assumed traditional scientific research practices. Compared with academic and pharmaceutical company researchers, CRO researchers are provided with little training, poor pay, are discouraged from exercising any scientific curiosity or initiative and, therefore, are prohibited from publishing on research products from their work within CROs (Mirowski, 2011). These conditions lead to particularly high employee turnover rates at CROs, raising important questions about the fragmentation of the scientific research process and the responsibility for legal liability for the accuracy, disclosure, and confidentiality of research results and analyses (Mirowski, 2011). CROs also help to effectively enforce private industry's limitations on disclosure and confidentiality of research results by releasing data only at the company's request (Mirowski, 2011).

5.3.2 Dissolution and disappearance of the traditional scientific author: An adverse event of corporate science

The nature of outsourced research and development (R&D), discovery, and clinical trial research, analysis, and reporting has increasingly led to the inevitable dissolution and disappearance of the traditional scientific author (Mirowski, 2001). Traditionally, scientific authors have collected, analyzed, interpreted, and have had access

to raw data, from which they develop their own interpretations and scientific academic articles (Healy & Cattell, 2003). Authorship in the corporate privatized version of science has undergone a profound modification in which the role of authors named in the bylines of published articles may have been limited to making a few revisions to previously ghostwritten manuscripts to which they were offered "guest" or "honorary" authorship (Mirowski & Van Horne, 2005; Moffatt & Elliott, 2007; Unknown, n.d.).

Medical ghostwriting is considered to be a service that is provided by medical writers (Mack, 2009) and occurs when manuscripts are crafted by, or on behalf of, drug companies. Drug companies may pay CROs to conduct their trials and analyze the collected data in-house. Drug companies may then outsource the writing of the manuscripts describing the results to medical writers at MWOs or MCCs (Cosgrove et al., 2016; Sismondo, 2007). Once a draft of the manuscript is completed, prominent physicians are recruited to sign their names onto the manuscripts (Unknown, 2005). One type of internal industry document from the Drug Industry Document Archive (DIDA), called "Publication Plan Tracking Reports", illustrates the processes undertaken by a MWO called DesignWrite when drafting the manuscripts and deciding which physicians to target for each ghostwritten article, whether recruiting these physicians was successful, which journal will be targeted for submission of the ghostwritten article, and, ultimately, determining whether the manuscript was submitted and accepted, accepted with revisions, or rejected (Unknown, 2005).

Another internal industry document, "Medical Education and Communications Plan for the Premarin Product Outline" (DesignWrite, 1996), outlines DesignWrite's proposed services to help a drug company, with which it had a contract, promote its

products. This document includes a typical timeline for ghost authorship of manuscripts (Table 5.1). Accompanying this timeline are 1996-1997 costs for pre-clinical manuscripts (US$10,000), clinical manuscripts (US$16,000), review articles (US$20,000), poster presentations (US$6,000), and journal supplements (US$175,000) (DesignWrite, 1996). The physicians who agree to be named in the byline of the manuscript as authors are termed "guest authors" or "honorary authors". Once these articles are published as part of the peer-reviewed medical literature, their conclusions affect the literature base and are used to promote drugs to physicians (Sismondo, 2007).

Typically, the involvement of drug companies, CROs, MWOs, and MCCs is neither acknowledged, nor indicated within the submitted manuscript or published paper. However, sometimes, a specific medical writer may be acknowledged within the published paper, though this acknowledgement tends to be ambiguous, for instance, "editorial assistance" (Fugh-Berman, 2010) or "'We thank XX' (without specifying for what) or 'XX provided editorial assistance' (a euphemism, usually without affiliation, for 'XX from Company YY wrote the paper')" (Gotzsche et al., 2009). Although ghostwriting occurs across many fields and occurred prior to the development of CROs, medical ghostwriting in particular is important to study because the increase in medical ghostwriting has been in part attributed to the rise of CROs (Mirowski & Van Horne, 2005). Furthermore, the inherent intention of medical ghostwriting is to misguide and deceive readers about the origination of the work by carefully concealing industry's involvement in all aspects of the research and writing processes.

5.3.3 Ghost management, publication planning, and medical ghostwriting

The privatization and commercialization of the scientific research process has fostered an environment in which the process of R&D, discovery, clinical trials and their management, data collection and analysis, and writing of manuscripts has become so fragmented that it requires its own management structure. Ghost management describes the process wherein "…pharmaceutical companies and their agents control or shape multiple steps in the research, analysis, writing, and publication of articles" (Sismondo, 2007). Resultant articles are considered to be "ghosted" because the roles of drug companies, CROs, and MWOs in this process are generally invisible. The presence of the guest authors, in lieu of companies as the authors or disclosures of the companies' roles, paints these corporate research and review articles with a mask of independence and credibility (Sismondo, 2007). These articles are also considered to be "managed" because the companies, whose roles are invisible in the process of producing articles, shape the common message(s) communicated in the single article, or multiple articles, through a process called "publication planning" (Fugh-Berman & Dodgson, 2008; Sismondo, 2007).

Access to the DIDA, scholarly analyses of its documents, and written accounts and analyses of industry employees' experiences have provided a unique window into previously confidential daily practices in which industry and guest authors engage. In the context of corporate science in the pharmaceutical industry, publication planning refers to an organizational timeline and plan that governs the dissemination of clinical information into the medical literature through a finely calibrated process that determines the writing and release of clinical trials, commentaries, research articles, and review articles

concerning a particular product (Fugh-Berman & Dodgson, 2008). According to a legal deposition from a senior medical writer from DesignWrite, publication plans and strategies reflect the objectives of the sponsoring company and not the MWO that is contracted to produce the manuscript for publication (Unknown, 2006). This senior medical writer explained that the objectives of publication plans, to sell more drugs, were in the domain of the sales and business teams and were not necessarily clear to the writers. However, opposing counsel showed that the involvement of medical writers is often more extensive. Counsel provided a document prepared by DesignWrite called "Medical Education and Communications Plan For The Premarin Product Line", which indicates that at least some writers at DesignWrite were tasked with developing a marketing plan for the sponsor's product (Unknown, 2006). This document states that:

> DesignWrite is pleased to offer its medical education and communications services to [the drug company] to aid in promoting the array of Premarin products. Our expertise and extensive experience in the organization and development of scientific and technical communications, in addition to our strategic marketing capabilities, will prove invaluable in support of the brands (DesignWrite, 1996).

The senior medical writer agreed that DesignWrite was contracted by a drug company to prepare proposals for publication plans and that "…these were prepared in the ordinary course of business by DesignWrite and then submitted to [the drug company]" (Unknown, 2006).

From the perspective of pharmaceutical companies, research is sometimes used to increase brand recognition. When research and brand recognition are both considered to be part of the marketing for drugs, the research that pharmaceutical companies conduct must demonstrate the effectiveness of their products (Sismondo, 2004). When industry-sponsored clinical trials, secondary review articles, editorials, and comments are

published in medical journals, they serve to draw attention to the manufacturers' products. The role of ghost authors, in this scenario, is to craft manuscripts that are favourable to the drug company that commissioned the paper (Sismondo, 2004). While ghost authors typically remain anonymous in the process, guest authors sign their names to the byline as authors of the papers. The publications are viewed as self-promotion and self-marketing because they contribute to professional prestige (Sismondo, 2004). The end result of a successfully ghost-managed and ghost-written manuscript is a published article in an influential journal with an appropriate target audience for the sponsor's product, with no clear indication that the clinical trial was perhaps conducted by a CRO and that the manuscript was written by a MWO or MCC.

The secrecy associated with industry's involvement in the research, analysis, and writing processes affords the pharmaceutical industry substantial influence over not only the research process, but also the ways in which it is used as a vector of MBM (Sismondo, 2007). Ghost management amplifies the already present sponsorship bias because the unidirectionality of motivations and influence by corporate sponsors on the research imposes controls on the writing and publication stages of article development. Corporate influence can be effectively exerted at every phase of the publishing process. The ensuing published article biases medical opinion, practice, and the treatment decisions that affect patients (Sismondo, 2007). The people who coordinate this process, publication planners, are supported and represented by the International Publication Planning Association (IPPA) and the International Society for Medical Publication Professionals (ISMPP) (Fugh-Berman & Dodgson, 2008). The ISMPP now has over 1,400 members (ISMPP 2015). Ghost management and publication planning allow industry to control both the

production and release of pre-clinical and clinical trials, research articles, review articles, and commentaries that may be published years before the sponsor's drug is launched (Fugh-Berman & Dodgson, 2008). Sismondo and Doucet (2010) state that it is reasonable to estimate that approximately 40 percent of journal articles pertaining to clinical trials of new drugs are ghost managed. When these articles are added to published meeting presentations on clinical trials, the percentage could be even higher.

5.3.4 The roles and publishing interests of medical journals

Just as the pharmaceutical industry operates in the private sector, so too do medical journals. Substantial medical journal income comes from publishing articles and supplements for which sponsoring companies will purchase reprints (Smith, 2003). Although medical journal editors may insist that they are unaware of ghost management, publication planning, and ghost writing practices, Mirowski (2011) argues that the editors of all major medical journals are aware that these practices occur. Sismondo and Doucet (2010) provide an account of medical journal editors of three of the most highly regarded medical journals, one representative of a journal editors organization, and a representative of a major international publisher of several journals who were all in attendance at an ISMPP meeting. Other publishers and journals promoted themselves at booths at the trade show associated with the ISMPP meeting (Sismondo & Doucet, 2010). The editors understood the role of the ISMPP members in the audience and it became clear that regular communication between publication planners and journal editors was the norm (Sismondo & Doucet, 2010); therefore, medical journals may be complicit in permitting the practices

of ghost management and publication planning to continue as ordinary business practices. A journal editor even "…expressed appreciation for medical writers" and provided advice to medical writers to make the submission process run more smoothly (Sismondo & Doucet, 2010).

Journal editors may also correspond with medical writers instead of the authors listed in the byline (Sismondo & Doucet, 2010). Correspondences with medical writers who manage manuscripts may indicate to editors that these manuscripts are some of the most important pieces that the editors will accept for publication. Determination of manuscript importance is based, in large part, on whether the manuscripts, once published, will be well-cited compared to others on the same topic, considering that publication planners are likely to cite previously published articles that were ghostwritten. Moreover, if a manuscript is being managed by publication planners, then the manuscript is important to the commissioning company and its publication will likely lead to the purchase of reprints that will be distributed by sales representatives to doctors (Sismondo & Doucet, 2010). Medical journals are not considered to be promotional material by governmental regulatory agencies and, so, do not fall within their jurisdictions; therefore, the interpretation of data and potentially embedded promotional messages in published articles, are not subject to government regulation (Fugh-Berman & Dodgson, 2008). The important role of medical journals to publication planners and their corporate objectives can be illustrated by an account of an industry consultant, who had previously worked in government. This consultant cautioned at an ISMPP meeting that if regulators saw publication plans, they would be forced to regulate these practices because some

publication strategies explain the intent of publication planners to promote drugs off-label (Sismondo, 2011).

Richard Smith, past-editor of *British Medical Journal*, argues in his suitably titled article, *Medical Journals are an Extension of the Marketing Arm of Pharmaceutical Companies*, that favourable clinical trials published in medical journals are among the most profitable forms of advertising for companies because these trials are perceived by physicians as the highest form of evidence and possess the journal's "stamp of approval" (Smith, 2005). A positive clinical trial that is published in a reputable peer-reviewed medical journal can be worth thousands of pages in advertising and may also be endorsed in accompanying press releases from the medical journal as well as the public relations and medical education firms hired by the sponsoring company (Smith, 2005). Published articles also provide the literature on which advertising and promotional materials can be legitimately based in order to position a product and serve as the foundation for secondary and review articles (Fugh-Berman & Dodgson, 2008).

Marcia Angell, past-editor of *New England Journal of Medicine*, has described peer-review as part of a "broken system" of pharmaceutical research and regulation (Angell, 2008). Richard Horton, current editor of *Lancet*, has stated that "journals have devolved into information laundering operations for the pharmaceutical industry" (Smith, 2005). The peer-review process has been unable to serve as a safeguard against publishing clinical research and related scientific studies that are written with the intention to promote industry's commercial objectives at the expense of public health, data transparency, and true critical analysis of the best available clinical evidence.

Corporate scientific practices that have been undertaken by the pharmaceutical industry in the interest of profit have attracted the attention of researchers in the fields of social science (see Dana & Lowenstein, 2003; Rosenberg & Allard, 2008; Sismondo, 2009), science and technology studies (see Lave et al., 2010; Mirowski, 2011; Packard, 1996; Sismondo, 2003, 2011), medicine (see Fugh-Berman & Ahari, 2007; Fugh-Berman, 2010, 2013; Gagnon & Lexchin, 2008; Lexchin, 2008, 2012; Persaud, 2013; Ross et al., 2008; Steinman, Bero, Chren, & Landefeld, 2006), law and ethics (see Bosch, Esfandiari, et al., 2012; Braithwaite, 1984; Elliott, 2004, 2010; Gagnon, 2013; Lemmens & Waring, 2006; Lemmens, 2000; Spielmans & Parry, 2010; Stern & Lemmens, 2011), and medical anthropology (Oldani, 2004; van der Geest, Reynolds White, & Hardon, 1996). This body of literature, concerned with pharmaceutical industry practices, has grown in size and breadth over time due to increasing access to industry insiders and internal industry documents. Access to these materials has provided researchers with a window into the culture of scientific research, writing, and publishing in the pharmaceutical industry. In their works, these and other researchers have individually introduced a number of terms that have traditional meanings that differ from the meaning that is attributed to them in the context of corporate scientific publishing, and in addition have added to the lexicon other terms that describe the various roles in the medical research and publication processes.

Rochon and colleagues (2010) provide a glossary of 13 terms, which accompanies a four-section FCOI checklist with 15 items. The authors intend the glossary and checklist to be used together for specific clinical research studies by the investigators and study team members including study coordinators, research assistants, and study nurses

(Rochon et al., 2010). This paper expands on and broadens the scope of the study by Rochon and colleagues by presenting a glossary and assessment tool that, together, focus on transparency within the research and publications processes in an effort to uphold the academic and scientific integrity of published medical journal articles. The remaining sections of this paper provide the methodology for creating a glossary or compendium of terms including first, a definition of each term followed by, in most cases, quotations by academics on their research into the publishing practices within the pharmaceutical industry. The quotes are valuable insofar as they illustrate the current usage and perspectives on the relevance of the terms. The glossary provides a snapshot of documented practices and academic analyses of them that can be used to understand the normative research practices in corporate science. Drawing from the glossary, the assessment tool attempts to take a measured, step-wise, process-oriented view of research and publishing, informed by the importance for transparency in the medical research and publications processes. The assessment tool loosely mirrors the glossary in that it comprises three categories and many of the terms from the glossary. The assessment tool is informed by the checklist by Rochon and colleagues (2010) as well as terms in the glossary.

5.4 METHODOLOGY

5.4.1 Analyzing discourse using thick description and textual analysis

"Thick description" is an anthropological methodology that allows the researcher to be both theoretical and analytical with the purpose of describing both abstract and

general patterns, as well as characteristics of social interactions, in a particular culture (Holloway *in* Ponterotto, 2006). Thick description interrogates the significance of actions and behaviours, experiences, sequences of events, voices of those participating, and the meanings of their actions (Denzin *in* Ponterotto, 2006). Thick description requires social actions and interactions to be interpreted according to circumstances, meanings, intentions, strategies, and motivations (Schwandt *in* Ponterotto, 2006). The ability for description to be interpreted within the appropriate context, in this case neoliberal science, makes it "thick". In contrast, "thin description" allows only for a superficial account, limiting the abilities of researchers to interrogate underlying cultural significance (Holloway *in* Ponterotto, 2006).

Although thick description has typically been used by anthropologists conducting ethnographic work, most commonly to inform participant observation, use of this methodology can be expanded to qualitative research in non-anthropological fields (Denzin *in* Ponterotto, 2006). For example, thick description as a methodology for textual analysis can allow a researcher to probe, at a deeper level, the actions and behaviours portrayed within the literature to reveal meanings and social discourse. The simultaneous use of thick description and textual analysis allows for the examination of both concepts and the relationships between them, creating a "web of meaning" (Carley, 1993). Therefore, this study borrows aspects of thick description that have allowed for the collection of definitions from the literature without necessarily having to cut out or paraphrase to shorten the definitions to prevent any obfuscation. Although thick description is usually used to portray interviews with research participants, it is used here because the ways that authors phrase and develop their definitions is important to

document. Nuances and meanings of the terms are reflected in the definitions as phrased by the authors and paraphrasing would risk loss of those nuances. The ways that the two or more definitions for each term fit together is also important and, so, thick description is used not only as a methodology, but also as a tool of analysis.

The literature search was conducted through repeated online searches for internal documents, scholarly literature, and finding additional literature using the reference lists of this initial literature. A broad collection of literature was assembled between November 2014 and November 2015, using a combination of key terms including, but not limited to, "pharmaceutical" and "drug" with "company" and "firm", "physicians" and "doctors", "conflicts of interest", "financial conflicts of interest", "medical ghostwriting" and "ghostwriting", "litigation", "human rights", "access", "medical education", "medical journals", "clinical trials", "data sharing", "data transparency", "industry funding", "drug company funding", "publication", "published results", and "policy" or "policies". A variety of books, peer-reviewed articles, industry documents, and other materials were also suggested by colleagues between 2009 and 2015.

Approximately 300 sources concerning medical journal publishing practices in the areas of FCOI relationships, authorship and roles in publishing, and methods by which industry has masked its role in the research and publication processes were reviewed for this study. As in Lexchin et al. (2008), an instrument to extract key terms and their relevance to neoliberal science was developed to include the following domains: "Glossary Item", "ID Number", "Relevance", and "Thematic Category". The thematic category of each term was determined *a posteriori*. Using this instrument, one author reviewed the documents for language or terms that had either or both of the following

characteristics: (i) traditional meanings that differ from the meaning that is attributed to them in the context of corporate scientific publishing, or (ii) have been recognized within the published literature to be important in the context of transparency and FCOI disclosure in medical research settings.

Alongside compiling these terms, the relevance of each term to the culture of scientific research was recorded within the glossary. As opposed to developing the categories and terminology to be included within the glossary *a priori*, the collection of data was informed by emergent categories, which allowed for the progressive identification of analytical categories as they emerge from the data (Pope, Ziebland, & Mays, 2000; Steinman et al., 2006). The glossary items were systematically collected and documented and, subsequently, grouped into core thematic categories. Accordingly, neither the glossary items, nor categories were predefined. Based on the interpretation of saturation by Padgett (2012), the collection of glossary terms and relevant content for each item within the glossary were considered to have reached saturation when analyzing additional literature was redundant and revealed no new information than that which had been collected from the already reviewed literature. Multiple supporting quotations for each term are provided in an effort to achieve comprehensiveness and an accurate reflection of both the literature and the layers of complexity associated with the corporate research and publishing practices.

Thick description calls for the adequate presentation of the "voice" of participants by including long quotes or excerpts from the participants (Ponterotto, 2006), which are, in this case, the literature sources that engage in academic conversation by virtue of their public availability or being published. Engagement with this literature has allowed not

only for the definition of terms, but also for the development of an assessment tool. The glossary terms that could be assessed as part of a step-wise process of medical research and publishing (i.e., involvement of CROs, MWOs, or MCCs, authority over study protocols and content in manuscript) in addition to FCOI relationship disclosures were included in the tool. Where academic characterizations of corporate scientific processes were comprised of series of smaller steps (i.e., medical ghostwriting, ghost management), those terms were broken down into those steps in the tool. In this way, this instrument is evidence-based.

One author consolidated the glossary terminology and developed the assessment tool, which were then reviewed by five experts (see Acknowledgements). Because this study was based on publicly available information, ethics review was not required.

5.5 FINDINGS

5.5.1 Glossary

In total, the glossary comprises 50 terms, some of which represent academic interpretations of practices that have been used by drug companies to meet the needs of commercial science, sometimes at the expense of the public good. These 50 terms were identified and extracted from 118 sources, which ranged in date from 1993-2015. Each of these 50 terms were thematically categorized in the glossary into four core categories: “Category A: Financial conflict of interest disclosures for authors, research team, and other contributors”, “Category B: Roles in the research, writing, and publication

processes", "Category C: Data sharing and data transparency", and "Category D: Enforcement" (5.11 Appendix A). In each category, each term is accompanied by its "relevance" to medical journal publishing and relationships with the pharmaceutical industry and "support" in the form of direct quotes from the literature. Terms are also cross-referenced with each other where applicable.

5.5.1.1 Category A: Financial conflict of interest disclosures for authors, research team, and other contributors

Category A comprises 23 terms (I.D. #1-23) that describe various roles, relationships, and activities in which academic and practicing physicians may engage that have the potential to alter professional behaviours. These 23 terms include FCOI relationships such as receiving gifts and meals, honoraria, samples, grants, stock ownership, engaging in consulting relationships or industry-funded speaking relationships/speakers' bureaus, continuing medical education, employment at a drug company or subsidiary, seeing sales representatives, practice management consultants, acting as a key opinion leader (KOL), and providing paid expert testimony in a court case. The final item in Category A (I.D. #23) explores the extent to which transparency of FCOI disclosures are required by medical journal policies. In Category A, each of the 23 terms are supported by 1 to 7 excerpts from the literature (5.11 Appendix A).

5.5.1.2 Category B: Roles in the research, writing, and publication processes

Category B comprises 14 terms (I.D. #24-37) that describe a range of roles and processes in which physicians and drug companies have been reported to engage in the

current culture of corporate scientific research and publishing. These 14 terms include the roles of medical writers, medical ghostwriters, the involvement of CROs, MWOs, and MCCs. The academic analyses of corporate scientific processes described in this category include medical ghostwriting, publication planning, and ghost management. The final item in Category B (I.D., #37) explores the roles and degrees to which named authors as well as whether research, writing, or communication companies are involved in the research, writing, and publications processes. These 14 terms in Category B are each supported by 1 to 14 excerpts from the literature (5.11 Appendix A).

5.5.1.3 Category C: Data sharing and data transparency

Category C comprises 11 terms (I.D. #38-48) that explore the extent to which the named authors on publications own, control, and have access to the data on which they are publishing in a given manuscript submitted to medical journals. These 11 terms include clinical trial registration, ownership of data, data sharing, origination of data, prepublication review and study alteration, seeding trials, and the selective reporting of trials. The 11 terms in Category C were supported by 1 to 6 excerpts from the literature.

5.5.1.4 Category D: Enforcement

Category D comprises two types of sanctions (I.D. #49-50) for extreme violations of medical journal policies identified in the literature. The first type of sanction is a ban from publishing or acting as a peer-reviewer for that journal. The second type of sanction is the retraction of an article in an effort to correct the literature, should the

published information be significantly and deliberately misleading or falsified. Each of these two types of sanctions are supported by 2 excerpts from the literature.

5.5.2 Assessment tool

The assessment tool comprises three categories including “Category A: Financial conflict of interest disclosures for authors, research team, and other contributors”, “Category B: Roles in the research, writing, and publication processes”, and “Category C: Enforcement and sanctions” (5.12 Appendix B). In total, the assessment tool comprises 62 items, which are divided into the aforementioned categories. This assessment tool can be used by researchers to determine the types of financial relationships, the involvement of individuals, organizations, and companies in the research and publication processes, and the presence of enforceable sanctions in medical journal policies. By extension, analyses using this tool may also highlight the categories and terms that are not required by policies to be disclosed.

5.5.2.1 Category A: Financial conflict of interest disclosures for authors, research team, and other contributors

There are 23 terms (I.D. #A1-A23) in Category A in the assessment tool. The assessment tool terms in Category A closely parallel those in Category A of the glossary. For terms representing FCOI relationships in Category A, the assessment tool asks whether a journal’s policies require the disclosure of these relationships in present only, in the past 1-5 years, 6-10 years, or 10+ years. The assessment tool also asks whether the institutions or companies with which each of these FCOI relationships were affiliated are

required to be disclosed and if these disclosures and institutions are publicly accessible (5.12 Appendix B).

5.5.2.2 Category B: Roles in the research, writing, and publication processes.

Category B is comprised of two sections. The first section (I.D. #B24-B37) includes roles that may be undertaken by authors, members of the research team, funders of studies, and employees of supporting entities including CROs and MWOs. For each of these roles, the assessment tool asks whether journal policies require disclosure of the presence of these roles, their start and end dates, and whether there was past participation in these roles. As in Category A, the assessment tool asks whether the institution or company at which authors and contributors engaged in these roles are disclosed and if these disclosures are to be made publicly accessible (5.12 Appendix B).

The second section of Category B (I.D. #B38-B59) attempts to discern whether the responsibility for, and involvement in, the steps of a study that is being submitted for publication are transparently identified. The items included in this section of Category B are informed by the glossary in addition to the FCOI checklist by Rochon and colleauges (2010). This section inquires about whether journal policies require disclosure of the party that has ultimate authority for the completion and approval of various components of the research process. Also based on Rochon and colleagues (2010), the ultimate authority for decisions throughout the research process was divided into four categories: study team, funder, shared responsibility, or unclear. The assessment tool also asks whether the policy requires the disclosure of the name of the institution or company at which the party with

ultimate authority is based, as well as whether this information is publicly accessible (5.12 Appendix B).

5.5.2.3 Category C: Enforcement and sanctions.

The final category in the assessment tool, Category C, comprises three items (I.D. #60-62). The items in this category seek to determine whether there is a party at the journal that is responsible for policy enforcement and whether there is a clear process by which the journal enforces the policy. Finally, this category provides a continuum of enforceable sanctions for noncompliance with, or violation of, journal policies. The sanctions range in severity from rejection of an article, to labeling an article with a "notice of correction", to retraction of a published article. The assessment tool asks whether these enforcement mechanisms and sanctions are clear with the options of "no", "unclear", and "yes". The assessment tool also inquires about whether the enforced sanctions are made public once they have been applied (5.12 Appendix B).

5.6 DISCUSSION

Based on the literature review, a glossary listing 50 terms was compiled. Each source was read iteratively and distilled into the glossary, then, from the glossary the assessment tool was developed. Because of the subjective nature of this process, the expert panel helped to review the validity of the assessment tool. Organized into four categories, the glossary identifies not only the relevance, but also quotes from the literature indicating

the importance of each term to the area of medical research and publishing. As is indicated in the glossary, many papers produced different reasons for the relevance of the terms to corporate science, disclosure and transparency, and ensuring the accurate reporting of EBM, rather than MBM.

The preeminent role of journals as the forum that physicians, research, medical students, and the public trust for important information on medical treatments, alongside the business-oriented environment in which medical research is conducted has informed this evaluative undertaking. The items in the glossary and assessment tool are important to consider both individually and collectively within the context of understanding of the processes of pharmaceutical research, publishing, and promotion. The glossary and assessment tool now need to be tested. The glossary informs the assessment tool, so when applying the tool, the terms should be defined according to the glossary. Therefore, these two documents should be used together.

Alongside the glossary, the assessment tool can be used to help researchers and journals identify which items in the tool are most likely to predict submissions that are biased as a result of FCOI relationships and to design journal policies accordingly. For example, peer-reviewers and editors at journals can identify manuscripts with characteristics that they suspect to be consistent with the marketing goals for a product (see Barbour et al., 2016). The editors could send the assessment tool to the authors of these articles to fill out and, subsequently, determine which items in the tool were positive. Positive identification of these key items, in consultation with the glossary, could then be used to recommend journal policy development or amendments to existing policies in those areas to effectively limit the potential for bias in manuscripts. Consultation with the

glossary helps to ensure that the meanings of the terms are being considered during, and informing, policy development.

5.7 LIMITATIONS

This study has some limitations. The glossary and scoring tool should be considered preliminary because there are likely to be additional key terms that are not addressed, but may surface in future research or litigation that requires the release of additional internal industry documents. The scoring tool may also contain items that are not needed. Although the literature review and glossary captured researchers' analyses of some documents from the DIDA, this study did not systematically analyze and extract terms from the internal industry documents that are currently available in the DIDA and this could, therefore, be the subject of future research. Additionally, the glossary and assessment tool are not constructed to evaluate the roles of medical journal editors, whose roles are crucial because the enforcement of journal policies on disclosure is largely voluntary (Goozner, 2004). One of the roles of journal editors is to review the disclosures submitted by prospective authors and then determine if their disclosed FCOI relationships are to be considered relevant to their submitted manuscripts, according to the standards of the particular journal (Goozner, 2004). Additionally, medical journal editors have been found to also have FCOI relationships with drug companies (Cosgrove et al., 2016) and the guidelines that may regulate the professional conduct and FCOI relationship disclosures of journal editors were not the subject of this study. Institutional FCOI relationships between journals' publishing companies and the pharmaceutical industry are

also not addressed in this study. Another point that is not addressed is whether journals publish detailed accounts of their sources of revenue. Finally, this study did not look into whether journals have a policy of monitoring compliance with their policies or a published method for re-evaluating and updating their policies.

5.8 CONCLUSION

Evidence of potential biasing of the medical literature through FCOI relationships and various research and publishing practices, such as medical ghostwriting, undermines the integrity of the authorship system and research published in journals. The DIDA houses documents that have provided clear evidence of ongoing corporate practices that extend into relationships between physicians, drug companies, medical research and writing organizations, the careful framing and shaping of research throughout the research and writing processes, and publishing decisions. From the internal industry documents in the DIDA, as well as the published literature on FCOI relationships in medicine, it is increasingly the case that these relationships and behaviours have become considered as normative. The glossary and accompanying assessment tool provided in this study provide an entry-point into comprehensively addressing these issues as they pertain to the specific research and publication practices of contemporary medical research.

Gotzsche and colleauges (2007) argue that ghostly practices could be substantially reduced, and transparency improved, if clear and enforceable authorship policies were developed and adopted. It can be further argued that issues surrounding FCOI disclosures, ghostly practices, and data suppression practices could be considerably

reduced if clear policies that required transparency pertaining to not only relationships, but also the step-wise research and writing processes were developed, adopted, and enforced. Developing this glossary and assessment tool to help develop effective medical journal policies in the areas of FCOI relationships, roles in publishing and writing, and data sharing and transparency is a step towards achieving a more transparent medical literature.

The language and terminology included within the glossary can be situated within a specific medical-scientific and social milieu that has, over time, shaped and been shaped by the neoliberal-oriented corporate culture in which modern medicine operates. This culture has had, and continues to have, important consequences for the dissemination and translation of scientific knowledge, as well as the construction of the evidence base on which physicians rely. Sismondo and Doucet (2010) argue that asking *why* and *how* medical journal articles have been published is equally as important as asking *if* the results have been published. Because commercial management of medical research redirects the orientation of research to comply with commercial goals and can corrupt the literature base (Lexchin, 2005; Turner et al., 2008), medical journals ought to ensure that the manuscripts that they publish are not only based on ethically sound research, but also managed independently from industry (Sismondo & Doucet, 2010). The continued relationships between drug companies, CROs, MWOs, MCCs, and physicians, and the resultant socially established codes, have become palpable. With increasing access to internal industry documents and analyses of reported experiences of industry insiders and whistleblowers' accounts, the industry's socially acceptable codes and behavioural norms are no longer adequate; however, even with exposure these practices persist. Medical

journals, as one source that is responsible for the dissemination of medical research, must transparently pay attention to the important nuances of corporate science and address and regulate deceitful publishing practices by the pharmaceutical, research, and writing industries.

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TABLE 5.1 TYPICAL WORK FLOW PLAN FOR DEVELOPING A MANUSCRIPT FOR SUBMISSION TO A PEER-REVIEWED JOURNAL. ADAPTED FROM INTERNAL INDUSTRY DOCUMENT (DESIGNWRITE, 1996)

Service provided/Action taken by DesignWrite	**Estimated Timeline**
Client provides data report	TBD
DesignWrite prepares outline	2 weeks
Client internal review	2 weeks
DesignWrite prepares first draft	4-8 weeks
Client internal review	2 weeks
DesignWrite addresses consolidated client comments (second draft)	2-3 weeks
Second draft reviewed by selected author	2 weeks
DesignWrite incorporates author comments (third draft)	2 weeks
DesignWrite assists in journal submission	2 weeks
Journal provides peer-reviewer comments	TBD
DesignWrite addresses comments; resubmits	2 weeks
Journal acceptance and publication	TBD

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5.11 APPENDIX A INDEX OF GLOSSARY TERMS AND GLOSSARY

5.11.1 INDEX OF GLOSSARY TERMS

5.11.2 GLOSSARY OF TERMS

CATEGORY A: FINANCIAL CONFLICT OF INTEREST DISCLOSURES

(1) COMPENSATION FOR LODGING, TRAVEL, TRANSPORTATION, ATTENDANCE, OR MEETING REGISTRATION FEES AT OFF-SITE LECTURES AND MEETINGS (I.E., FOR CONTINUING MEDICAL EDUCATION (CME) OR RESEARCH-RELATED ACTIVITIES, TRAVEL TO ADVISORY BOARDS, CONSULTATION, ASSISTANCE WITH GOING TO CONGRESS)

RELEVANCE:

Compensation for travel, accommodations, transportation, and meeting registration fees may be provided to physicians by drug companies for attending CME programs.

SUPPORT:

1. "The following list, while not exhaustive, indicates the interactions with industry that must be addressed (Blumenthal, 2004):… payment for attendance at lectures and conferences, including online activities; CME for which physicians pay no fee; payment for time while attending meetings; [and] payment for travel to meetings or scholarships to attend meetings" (Brennan et al., 2006).

2."…[C]onference travel funding [is] felt to exert more influence than promotional material does. Each interaction elicited ethical concerns; travel funding generated the most concern" (Wazana, 2000).

3."…[T]he temporal direction of the association was established for…the physician prescribing rate of the CME sponsor's drug (Bowman & Pearle, 1988); an increase in hospital prescribing rate of the conference travel sponsor's drug (Orlowski & Wateska, 1992)" (Wazana, 2000). Furthermore, "…the literature points to important concerns for…CME sponsorship, and conference travel" (Wazana, 2000).

(2) CONFERENCE MODERATORS

RELEVANCE:

Medical researchers or academic physicians may act as moderators during CME programs to facilitate the sessions. The moderator may receive guidance or instructions from a drug company either before or during the session in order to align the discussion with the commercial interests of the company.

SUPPORT:

1. Moderators may be medical researchers or physicians whose role in conferences is to facilitate CME sessions. Internal industry documents reveal a case in which a drug company helped to establish the agenda of an educational session and monitor teleconferences while they were in progress. These calls were organized through a medical education and communications company (MECC) "to discuss unapproved uses of gabapentin" and "an agenda was prepared for physician moderators directing them to discuss such topics as 'how [a drug] evolved into a first line therapy option in practice." In another series of teleconferences, which a third-party vendor was responsible for organizing, senior drug company employees "were invited to participate but told to 'instruct the teleconference operator that you should be in LISTEN ONLY mode and your name should NOT be announced during the introductions' (emphasis in original)." Internal industry documents also reveal that conference moderators "were paid $250 to $500 per call and had other financial ties to [the drug company]. For example, each of the 10 moderators from one series of calls requested or was allocated between $14,800 to $176,000 for participation in various [drug company]-sponsored activities between 1993 and 1997" (Steinman, Bero, Chren, & Landefeld, 2006).

*Cross-reference with Industry-funded speaking relationships/speakers' bureaus (#9)

(3) CONSULTING RELATIONSHIPS (EXCLUDING SCIENTIFIC RESEARCH AND SPEAKING ENGAGEMENTS)

RELEVANCE:

Physicians may be hired by drug companies to provide consultation services during which the physicians may help to advise the companies on their marketing strategies or to participate on scientific advisory boards.

SUPPORT:

1. Drug companies employ consultants, who may also be respected doctors and "key opinion leaders" or "thought leaders", to help advise on marketing strategies (Moynihan, 2008).

2. Consulting relationships can occur when physicians and medical research faculty are employed, or are under contractual agreement with one or more drug companies. These physicians and researchers might be asked to help advise the company on its marketing strategies for a particular drug, or to join advisory or consultation boards (sometimes called scientific advisory boards (SABs)), or to serve in these roles individually. Increasingly, pharmaceutical companies approach and engage physicians in their target markets in this capacity. Payments to physicians or researchers as advisors or consultants can lead to millions of dollars in profits per year for the sponsoring companies. Consulting relationships have become routine marketing expenses for pharmaceutical companies for which physicians take on a

promotional role in favour of the sponsor's product (Brandt and Hutzler, 2015; Canadian Medical Association [CMA], 2007; American Medical Student Association [AMSA], 2014).

3. When determining the valuation of a physician consultant agreement with a pharmaceutical company, some of the factors that are considered include the number of hours required, duties and responsibilities, complexity or simplicity of the duties and responsibilities required, level of leadership required, objectives and deliverables, and potential impact of the thought leader/consultant on organizational and/or product success. Valuation of qualifications of the physicians who are contracted as consultants depends on level of education, credentials, specialized training, professional certifications, leadership experience, academic appointments, research experience and funding history, invited presentations, publication history, and recognition in the healthcare community (Brandt and Hutzler, 2015).

*Cross-reference with Service on scientific advisory boards (SABs), consultants meetings, board of directors, review panels (#20)

(4) CONTINUING MEDICAL EDUCATION (CME)

RELEVANCE:

Continuing medical education (CME) refers to accredited educational programs in which physicians are typically required to enroll as part of their continuing education and professional development (American Medical Association [AMA], 2015; CMA, 2015). It is common for physicians to receive educational program support from the pharmaceutical industry (Choudhry, Stelfox, and Detsky, 2002).

SUPPORT:

1. "Doctors are required to maintain standards of medical practice by participation in CME, however this is made possible by funding from the marketing division of the pharmaceutical industry which has the NHS (National Health Service) as its major customer in the UK [United Kingdom]. The results from our study suggest that many doctors do rely on industry funding for CME. About half of the doctors attending conferences were funded by the industry and approximately one third of the doctors would not have attended the conferences if there had been no industry funding…While many doctors recognise the potential for the industry to influence their prescribing habits, few recognise that they themselves are susceptible" (Rutledge et al., 2003).

2. "In the business of medical communications, the term medical education covers a lot of ground. Most agencies work at least in part for the pharmaceutical and medical-device industries, for which they produce a whole range of educational and communications materials, from magazine articles and slide kits to podcasts and Webinars. Many agencies organize grand-rounds lectures at hospitals, recruiting speakers and preparing their slides. Some agencies help pharmaceutical companies train 'opinion leaders' and manage their speakers' bureaus. Most of them organize a number of live events, such as satellite symposia at conferences and advisory board meetings. A good proportion of this material is officially accredited as [CME] for physicians. Accredited CME has an enviable market niche; most physicians are required to take part in a certain number of CME events in order to maintain their licenses to practice. In the old days, CME was produced by universities and professional societies, and it was largely paid for by registration fees and the groups that were sponsoring it. Over time, however, the proportion of CME that is funded by the pharmaceutical and device industries has crept steadily upward. The sharpest uptick has occurred over the past 10 years or so. Between 1998 and 2006, commercial support for CME increased by a fourfold margin to a total of $1.2 billion. By 2006, over 60 percent of CME was funded by commercial sources. During the same period, profit margins for accredited CME providers increased nearly sixfold, from 5.5 percent to 31 percent, with total income reaching $2.38 billion" (Elliott, 2010).

3. "Most practicing physicians can afford to pay for their continuing education. If they are employed, subsidies for CME should be a fringe benefit. In addition, most professional institutions capable of providing CME can afford to provide it at cost, without subsidies from the pharmaceutical business…One important step is to recognize that CME must be clearly separated from pharmaceutical marketing. Physicians may even have to pay more for CME but then may value it more, demand higher quality, and learn more from it" (Relman, 2001).

4. "Support for CME comes from the marketing budget in most companies, and that budget must produce sales" (Relman, 2001).

5. A Parke-Davis business plan stated that "Medical education drives this market!!" (Unknown, 1996).

6. A 2011 study on off-label marketing of pharmaceuticals found that CME seminars have been "…organized with speakers known to promote off-label uses...In a few cases, whistleblowers reported that CME activities were organized by shell corporations to impart an appearance of scientific neutrality" (Kesselheim, Mello, and Studdert, 2011).

(5) EXTENDED FINANCIAL CONFLICT OF INTEREST DISCLOSURE (I.E., SPOUSES OR PARTNERS, ADULT CHILDREN, OTHER RELATIVES)

RELEVANCE:

The families of medical researchers or physicians may have financial interest in one or more drug companies. These extended relationships have the potential to influence the research choices made by physicians. Disclosures in this area should include receipt of payments salient to the drug or treatment or disease that is discussed in the publication.

SUPPORT:

1. In a documented case, a commercial ethics review board was owned by the wife of a drug testing firm, to which pharmaceutical companies outsourced their trials and there may have been undue influence on this review board to approve studies, despite trials being conducted in "ethically dubious conditions" and on vulnerable populations (Elliott, 2010; Evans, Smith, and Willen, 2005).

2. "Investigators must also disclose the financial interests of spouses and dependent children." Disclosure can extend to "… 'de facto spouses', parents, siblings, and adult children" (Lo, Wolf, and Berkeley, 2000).

(6) GIFTS AND MEALS

RELEVANCE:

Any material good that a pharmaceutical company, usually via a drug rep, gives to, and is accepted by, an author of any value. These may include, but are not limited to, notepads, medical supplies, prescription pads, pens, posters, refrigerator magnets, televisions for waiting rooms, calendars, books, meals, alcohol, sporting activities (i.e., golf games or gym memberships), sporting or theatre or musical event tickets, and vacations. Gifts can also include biomaterials, discretionary funds, and equipment.

SUPPORT:

1. "Giving consumers small gifts can alter their perceptions of a product. Salespeople have long used gifts to increase sales. Different kinds of gifts may have different effects. Large gifts may act more like bribes or kickbacks. Small ones may serve as advertising or samples. Large gifts seem more suspicious than small gifts. They lead one to ask: 'Why is the firm giving the gift, and what does it expect to get in return?' But small gifts can influence physicians as well, even if the monetary value of what is received is trivial. The notepad and pen or paperweight with the drug's name emblazoned on its side is a constant reminder of the product. Receiving such gifts may not act as a strong financial inducement to use the supplier's services, but it is an effective form of advertising. Moreover, no clear border divides gifts of value, which might compromise judgment, from gifts as advertisements. Thus, a case can be made for restricting even the smallest gifts" (Rodwin, 1993).

2. "The amount of money residents reported having received was positively correlated with their stating that they would have the same degree of contact with representatives if no promotional gifts were offered…Also, the number of promotional items received was positively correlated with the belief that discussions with representatives have no impact on prescribing behaviour" (Hodges, 1995).

3. "For decades the medical community has debated whether gifts and perks from reps have any real effect. Doctors insist that they do not. Studies in the medical literature indicate just the opposite. The pharmaceutical industry has managed this debate skillfully, pouring vast resources into gifts for doctors while simultaneously reassuring them that their integrity prevents them from being influenced"; however, "Over the past twenty years, the evidence that gifts and payments have a profound influence on doctors has become virtually indisputable. Doctors who are paid by a company are more likely to write prescriptions for that company's drugs, more likely to give talks that are favourable to the company, and more likely to produce research that benefits that company. Even modest gifts have a substantial effect…[T]he more industry ties a doctor had, the more likely that doctor was to request specific additions to the formulary. In fact, doctors who often accepted money for speaking engagements were almost thirty times more likely to ask for a specific drug to be added to the formulary than doctors who didn't" (Elliott, 2010).

4. "Researchers were aware that something was expected in return for the gift. Sponsor expectations that the gift be used for its intended purpose and not be re-gifted, and that the sponsor be acknowledged in publications, are certainly reasonable. Disturbingly, however, about a third (32%) of gift recipients reported that the funder wanted prepublication review of any articles or reports stemming from the use of the gift. This expectation was higher for gifts of biomaterials…Also, 44% of firms wanted assurances that the biomaterial was not to be used for applications that competed with company products" (Fugh-Berman, 2013).

*Cross-reference with Pharmaceutical industry sales representatives, drug reps, detailers, or medical science liaisons (#16)

(7) GRANTS: RESTRICTED AND UNRESTRICTED

RELEVANCE:

Grants are sums of money that are given or awarded to medical researchers or academic physicians in support of their research. Grants may also be awarded to medical schools and academic research centres for maintaining or adding resources. There are two types of grants: restricted and unrestricted. Restricted grants are typically donor-designated and earmarked toward a specific resource or research study, while unrestricted grants are generally unencumbered and free from any restrictions that may have been imposed by the donor.

SUPPORT:

1. "Increasingly, biomedical studies receive funding from commercial firms, private foundations, and government. The conditions of this funding have the potential to bias and otherwise discredit the research" (Davidoff et al., 2001).

2. "[Industry] [f]unding promotes study designs that are more likely to produce favourable results, such as designs involving: placebos or other poor comparators, inappropriate doses, carefully constructed experimental populations, poor surrogate endpoints, trial durations unlikely to show side effects, and definitions likely to show activity or unlikely to show side effects (Bekelman et al., 2003; Djulbegovic et al., 2000; Montori et al., 2004) (Sismondo, 2008a).

3. "Industry sponsored drug and device studies more often had favorable efficacy results…harms results…and overall conclusions… compared with non-industry sponsored drug and device studies…Our analysis suggests that industry sponsored drug and device studies are more often favorable to the sponsor's products that non-industry sponsored drug and device studies due to biases that cannot be explained by standard 'Risk of bias' assessment tools" (Lundh et al., 2012).

4. "A meta-analysis revealed that industry funding greatly increased the chances of pro-industry results…17 analyses published [between 2003 and 2008] have shown an association, typically a strong one, between industry support and published pro-industry results, and 2 have not. Taken in conjunction with the earlier systematic reviews that found 20 of 23 reports of positive associations, it is unequivocally the case that sponsorship influences published results" (Sismondo, 2008b).

5. An unrestricted grant is one example of a funding opportunity that companies provide in order to exert their influence on a program. Although unrestricted grants are thought to reduce the risk of bias, unrestricted grants may, in some cases, be favourable to companies. For example, a drug company "…funded educational programs through 'unrestricted educational grants' to medical education and communications companies [MECCs]…for-profit businesses that specialize in producing conferences for physicians on behalf of pharmaceutical manufacturers and are often subsidiaries of marketing firms. Under this 'unrestricted' arrangement, [this drug company] relinquished control over the program speakers and its content. This allowed programs organized by medical education companies to discuss unapproved uses of gabapentin and to grant continuing medical education accredit from the Accreditation Council of Continuing Medical Education (ACCME), neither of which is permissible for events directly sponsored by drug companies… Unrestricted grants were used to underwrite other forms of education including payments to physicians to cover the cost of attending conferences (United States ex rel. Franklin v. Parke-Davis). Another grant exceeding $300 000 funded the production, printing, and distribution of 75 000 copies of an epilepsy handbook, with half of this budget allocated to soliciting interest among and delivering books to high prescribers of anticonvulsant agents (United States ex rel. Franklin v. Parke-Davis)" (Steinman et al., 2006).

6. "Most COI policies assume that if industry money is pooled (i.e. not given directly to one individual but rather to an academic department whose chair oversees expenditures), the risk of bias is negated. Despite the fact that money is not given to one particular researcher, a climate is being created when pharmaceutical companies fund academic departments, and this climate is not neutral because any chairperson is cognizant of the potential for these pooled funds to be withdrawn if his/her department starts disseminating research findings that are not pro-industry" (Cosgrove and Bursztajn, 2010).

(8) HONORARIA AND PAYMENTS

RELEVANCE:

In the context of medicine, honoraria are defined as a payment that is made to a physician or academic medical researcher for services for which fees are not legally necessary, or payment of an amount that is more than is traditionally acceptable for a given task. Honoraria are typically not bound by a contractual agreement.

SUPPORT:

1. Internal industry "[d]ocuments were found describing [a drug company] compensating investigators with honoraria for agreeing to serve as authors on review manuscripts ghostwritten on their behalf by medical publishing companies. Honoraria varied, ranging from $750 to $2500.** One author refused his honorarium from Scientific Therapeutics Information stating, 'I really do not feel it is appropriate to be paid for this type of effort' (Cannon, 1999)" (Ross, Hill, Egilman, & Krumholz, 2008).

*Cross-reference with Key opinion leaders (KOLs) or thought leaders (#12), Payment for working on or enrolling patients in clinical trials (#15), Guest authors or honorary authors (#28)

**These amounts may be more than are usually acceptable or common.

(9) INDUSTRY-FUNDED SPEAKING RELATIONSHIPS/ SPEAKERS' BUREAUS

RELEVANCE:

Physicians may be paid US$500 to US$700 or more by drug companies to deliver lectures that were wholly or partially based on slides and information provided to the physicians by the companies.

SUPPORT:

1. A conflict of interest relationship that occurs when respected doctors are paid generous fees, for example US$500 or US$700 to US$2500 or US$3000, for delivering a single lecture that was largely or wholly based on slides supplied by the sponsoring company. In some cases, the sponsoring company would pay the speakers' fee to the academic centre which would, then, compensate the doctor. Often, those who are speaking are classified as "key opinion leaders" or "thought leaders". These speeches often take place at educational events sponsored by drug companies (Moynihan, 2008). Speakers' bureaus may be important physician-to-physician fora in which sales employees are "encouraged to expand the speaker base – identify and train strong [drug] advocates and users to speak locally for [the drug]" (Steinman et al., 2006). Speakers' bureaus for lecture series may also include chairs of departments and directors of clinical programs at major teaching hospitals that are relevant to the drug being promoted. These speakers may also be invited to special meetings in which they are "updated on

promotional strategies for the drug" (Steinman et al., 2006).

*Cross-reference with Conference moderators (#2)

(10) INDUSTRY SUPPORT FOR FUNDS FOR TRAINEES AND JUNIOR RESEARCHERS (I.E., SCHOLARSHIPS, AWARDS, FELLOWSHIPS)

RELEVANCE:

Scholarships, prizes, awards, and fellowships are financial means by which companies can garner pro-industry attitudes among the recipients. These financial mechanisms often require, or are accompanied by, a short-term or long-term relationship with the sponsor that is providing the financial opportunity.

SUPPORT:

1. "The following list, while not exhaustive, indicates the interactions with industry that must be addressed (Blumenthal, 2004): …scholarships to attend meetings and grants for research projects" (Brennan et al., 2006).

2. A 2013 study on conflict of interest policies at Canadian medical schools stated in its policy scoring tool that "[t]he policy must either prevent industry from earmarking or awarding funds to support the training of particular individuals (recipients must be chosen by the school or department), or the policy must mandate institutional review of the giving of funds" (Shnier et al. 2013).

(11) INSTITUTIONAL REVIEW BOARDS (IRBS) OR RESEARCH ETHICS BOARDS (REBS)

RELEVANCE:

Institutional review boards or research ethics boards are committees whose responsibility is to review and monitor research involving human subjects, for example, clinical trials. IRBs or REBs are able to approve, reject, or require revisions for research protocols. IRBs or REBs may be for-profit or not-for-profit.

SUPPORT:

1. "For the past three decades, institutional review boards, or IRBs [institutional review boards], have been the primary mechanism for protecting subjects in drug trials. FDA [Food and Drug Administration] regulations require that any study in support of a new drug be approved by an IRB. Until recently, IRBs were based in universities and teaching hospitals and were made up primarily of faculty members who volunteered to review the research studies being conducted in their own institutions. Now that most drug studies take place outside academic settings, research sponsors can submit their proposed studies to for-profit IRBs, which will review the ethics of a study in exchange for a fee. These boards are subject to the same financial pressures faced by virtually everyone in business. They compete for clients by promising a fast review. And if one for-profit concludes that a study is unethical, the sponsor can simply take it to another" (Elliott, 2010).

(12) KEY OPINION LEADERS (KOLS) OR THOUGHT LEADERS

RELEVANCE:

Key opinion leaders (KOLs), or thought leaders, are physicians who are recruited to serve as credible professionals who help to disseminate drug companies' messages to their professional circles. KOLs receive their information from the drug companies with which they work and disseminate only that information to their networks.

SUPPORT:

1."Today, the pharmaceutical industry uses the terms key opinion leader (KOL) and thought leader to refer to influential physicians, often academic researchers, who are especially effective at transmitting messages to their peers. Pharmaceutical companies hire KOLs to consult for them, to give lectures, and, occasionally, to make presentations on their behalf at regulatory meetings or hearings...KOLs do not exactly endorse drugs, at least not in ways that are too obvious, but their opinions can be used to market them – sometimes by word of mouth, but more often by quasi-academic activities such as grand-rounds lectures, sponsored symposia, and articles in medical journals. While pharmaceutical companies seek out high-status KOLs with impressive academic appointments, status is only one determinant of a KOL's influence. Just as important is the fact that a KOL is, at least in theory, independent...[KOLs appear] to be impartial" (Elliott, 2010).

2. "Key opinion leaders [are] salespeople for [drug companies]" and the sponsoring companies "routinely measure the return on [their] investment, by tracking prescriptions before and after their presentations" and "[i]f that speaker didn't make the impact the company was looking for, then [the company] wouldn't invite them back". Drug company marketing staff are encouraged to not only find and recruit respected doctors, but also work regularly with these doctors to develop and mould them into "product champions". Sponsoring companies develop relationships with local and national opinion, or thought, leaders, who are respected doctors, to be used by drug companies to "help drug companies sell drugs" and "are engaged by industry to advise on marketing and help boost sales of new medicines [in] all specialties, in hospitals and universities" and communicate these pro-sponsor messages to the public. Drug companies maintain central databases of opinion leaders and have developed software to measure the effectiveness of their communications by calculating their return on investment. Key opinion, or thought, leaders are important because they can "influence thousands of prescribers and hence prescriptions through their research, lectures, publications and their participation on advisory boards, committees, editorial boards, professional societies and guideline/consensus document development. These recruited doctors are often senior in their positions

and "become an integral part of the company's marketing, education, and research strategies." Senior doctors with long-term financial relationships with drug companies are typically free to speak about medicines other than those that they are hired to promote in order to appear balanced (Moynihan, 2008).

3. "Another important trick of the trade is to maintain central databases of opinion leaders. Some small firms even offer special web-based software to keep track of opinion leaders and show their return on investment (KOL, n.d.). One firm offering such software, called KOL, specialises in managing opinion leaders for drug companies. Its website states that although these 'thought leaders' in the profession 'may not write prescription,' they can 'influence thousands of prescribers and hence prescriptions through their research, lectures, publications and their participation on advisory boards, committees, editorial boards, professional societies and guideline/consensus document development' (KOL, n.d.)" (Moynihan, 2008).

4. "In the complex and competitive world of healthcare marketing, Key Opinion Leaders (KOLs) play a significant role in influencing the perception and opinion of various stakeholders. While large marketing dollars are spent on shaping that influence, the impact and reach of such influential opinions can be directly associated to the rigor of generating the right influencer pool" (GenPact, 2012).

5. "To market Neurontin off-label, the company employed a variety of schemes, most involving a combination of rep ingenuity and payments to KOLs. Some KOLs signed ghostwritten journal articles. One received more than $300,000 to speak about Neurontin at conferences. Others were paid just to listen. (Simply having some of your KOLs in attendance at a dinner meeting is valuable...because thought leaders will often bring up off-label uses of a drug without having to be prompted" (Elliott, 2010).

6. KOLs are identified for given therapeutic areas and geographic regions for the client, or pharmaceutical company, by tracking companies that use positional, bibliometric, and sociometric analyses. Once identified, KOLs are tracked by companies which have developed specialized electronic KOL tracking systems. These tracking systems allow pharmaceutical companies to merge their existing data on their KOLs with online data on their KOLs from the internet, social media, and thousands of public sources. KOL tracking systems allow pharmaceutical companies to obtain real-time profiles on their KOLs that include research topics, KOL type, personal and professional interests, affiliations, academic standing, publications, committee and group involvement, involvement on treatment guidelines, speaking engagements, presentations to congress or government equivalents, involvement in clinical trials, activities in hospitals and tertiary centres, network reach and influence, research and clinical experience, and education information. Additionally, KOLs' past programs and engagements, historical interactions and return on investment, surveys and feedbacks, and preferred channels and content, web and social media activity, and news and web mentions are collected and analyzed in these tracking systems in order to rank and score the influence level of each KOL (YibLab, 2015; FirstWord, 2010; GenPact, 2012). These software systems for managing KOLs who are "…constructed and regulated with respect to what they study, where they go, what they say and write, and with whom they interact. Networks among KOLs, and between KOLs and other scientists and clinicians, are influenced by who is invited to sit on advisory boards, supervise clinical trials and speak at meetings. Within the KOL caste there is a structure and hierarchy, beginning with new blood and 'rising stars' and culminating with the grandees. KOLs considered sympathetic to a product are sometimes described as 'friends'; those thought overly anxious to offer endorsement for rewards may be light-heartedly referred to as 'tarts'. Importantly, KOLs are not biased and typically are excellent scientists and clinicians who do not compromise their beliefs, but are approached because their research interests converge with those of the company" (Matheson, 2008); however, "…academic authors groomed as [KOLs] may be used not only to endorse publications, but also to convey the impression the publications were originated by academics" (Matheson, 2011).

7. "Key opinion leaders were salespeople for us, and we would routinely measure the return on our investment, by tracking prescriptions before and after their presentations…I would give them all of the information that I wanted them to talk about. I would give them the slides. They would go through specific training programs on what to say, what not to say, how to answer specific questions, so that it would be beneficial to my company" (Moynihan, 2008).

*Cross-reference with Honoraria and payments (#8), Paid expert testimony in court case (#13)

(13) PAID EXPERT TESTIMONY IN COURT CASE

RELEVANCE:

An expert witness is typically a paid consultant who becomes involved in a legal case at the request of a lawyer, judge, or litigant. The payment that an expert witness receives for work done in this role becomes a financial conflict of interest if he/she becomes an author of a medical journal article that evaluates a treatment about or against which he/she testified.

SUPPORT:

1. "Financial relationships (such as…paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and of science itself…Editors should publish this information if they believe it will be important to readers judging the manuscript" (Davidoff et al., 2001).

2. Regulatory approval of a drug can sometimes be "…contingent upon expert testimony" that concludes that a certain category of disease ought to be considered as a distinct clinical entity to be included

as a disorder in the relevant guidelines (Cosgrove et al., 2006).

*Cross reference with Key opinion leaders (KOLs) and thought leaders (#12)

(14) PATENTS

RELEVANCE:

Medical researchers, physicians, their home research institutions, or the companies for which they work may possess patents. Depending on the patent holder and the agreement, the researchers, physicians, institutions, or companies may have financial interests in pursuing research on the patented technology.

SUPPORT:

1. "Circumstances in which an author holds a patent or performs a diagnostic or therapeutic intervention that is well-compensated, or in the content of the article being considered could influence the monetary value of some piece of medical knowledge" (Knopman et al., 2011).

2. "Any patents that are still active should also be disclosed as well as patent applications and intentions to apply for patents" (Goozner, 2004).

(15) PAYMENT FOR WORKING ON OR ENROLLING PATIENTS IN CLINICAL TRIALS

RELVANCE:

Doctors may work for drug companies on clinical trials and may be paid more than £200 per hour (Moynihan, 2008).

SUPPORT:

1. "Manufacturers recruited physicians to conduct clinical trials for them with the intent of encouraging off-label use ("seeding trials"), rather than for any useful scientific or information-gathering reasons" (Kesselheim, Mello, and Studdert, 2011). "Marketing departments are involved because a considerable number of Phase IV trials are designed to familiarize physicians with products, to encourage prescriptions, or to allow drug representatives more access to prescribers. For example, 'seeding trials' pay physicians to prescribe specific drugs as part of trials but are aimed at increasing prescriptions. Thus, pharmaceutical companies also support research by non-academic physicians…According to one internal document, a goal of the trial was to allow physicians to '[g]ain experience with [the drug] prior to and during the critical launch phase.' For this reason, the trial aimed to enroll 600 primary care physicians rather than a specific number of patients. The prescriptions of those physicians were tracked and compared with a control group of 99 physicians not in the trial. To the extent that data mattered, it was sales data; however, the company presented the trial to physicians as scientific research" (Sismondo, 2011).

2. "In 1994, according to the Tufts Center for Drug Development, 70 percent of clinical researchers were affiliated with academic medical centers; by 2006 that figure had dropped to 36 percent. The work can be lucrative and some sponsors offer researchers additional financial incentives to recruit subjects. One doctor told the Department of Health and Human Services that he was offered twelve thousand dollars for each subject that he could enroll in a trial, plus a thirty-thousand-dollar bonus and an additional six thousand dollars per subject after the first six." University departments out of which clinical trials are run have also received hundreds of thousands of dollars from industry, while the principal investigators and co-investigators of these trials have been paid over $500,000 from industry (Elliott, 2010).

3. "CROs [contract research organizations] sometimes pay recruitment fees to physicians of US$12,500 or more per subject" (Mirowski and Van Horne, 2005).

4. "Cash payments can potentially influence doctors' motives for joining a clinical trial. Some trials are designed by clinicians, often working with patients (Unknown, 2001), to answer important clinical questions. Other trials, especially in general practice, are different. They are sponsored and funded by pharmaceutical companies and are designed to achieve objectives that are at least in part commercially determined. Doctors who join have little or no control over the research question, design, methods, safety monitoring, analysis, reporting, or even the decision whether or not to publish the results (Unknown, 2001). Such trials depend on paying doctors to recruit patients. The size of the payment and not the buzz of research is what motivates doctors to join such trials" (Rao and Sant Cassia, 2002).

"Over the years we have seen the payments on offer soar to thousands of pounds per completed patient. Well organised British general practices can earn an extra £15 000 annually for three hours' work a week (Unknown, 1996)" (Rao and Sant Cassia, 2002).

"As a result, trials designed by non-commercial sponsors aiming to answer clinically important questions but without the funding available to pay recruiters fail to attract doctors (Wilson, Delaney, Roalfe & Hobbs, 1999). So called postmarketing research (phase IV) studies is the biggest culprit. As uncontrolled observational cohort studies, these studies make no attempt to address important areas of clinical uncertainty. Their stated purpose is to familiarise doctors with new and recently licensed drugs (La Puma et al., 1995). This is marketing thinly disguised as research and is greatly helped by—and probably not possible without—a system of undisclosed payments" (Rao and Sant Cassia, 2002).

"A system that allows commercially driven and clinically dubious research to crowd out good and much needed clinical trials, and that denies patients the opportunity to put their altruism to the best possible use, is unethical and unacceptable…Payments often overtly on a per capita basis, have reached levels that are of serious concern to

research ethics committees. Commercial sponsors regularly flout the implicit ban on per capita payments by claiming to pay for the work involved in conducting the trial (rather than for recruiting patients), and then overestimating the amount of time required for each patient. Such payments are in addition to the doctor's regular income and can result either in overwork or in displacing other more pressing clinical activity" (Rao and Sant Cassia, 2002).

*Cross-reference with Honoraria and payments (#8)

(16) PHARMACEUTICAL INDUSTRY SALES REPRESENTATIVES, DRUG REPS, DETAILERS, OR MEDICAL SCIENCE LIAISONS

RELEVANCE:

Pharmaceutical industry sales representatives, or drug reps, are employees of drug companies whose job is to increase sales of his/her employer's products (Elliott, 2010).

SUPPORT:

1. "To 'detail' a doctor is to give that doctor information about a company's new drugs with the aim of persuading the doctor to prescribe them…Drug reps today are often young, well groomed, and strikingly good-looking. Many are women. They are usually affable and sometimes very smart. Many give off a kind of glow, as if they have just emerged from a spa or salon. And they are always, hands down, the best-dressed people in the hospital. Drug reps have been calling on doctors since the mid-nineteenth century, but during the late 1990s their numbers increased dramatically. From 1996 to 2001 the pharmaceutical sales force in America doubled, to a total of 90,000 reps. By 2005, there was a drug rep for every 2.5 doctors in America. One reason is simple: good reps move product. Detailing is expensive, but almost all practicing doctors see reps at least occasionally, and many doctors say they find reps useful. One study found that for drugs introduced after 1997 with revenues exceeding $200 million a year, the average return for each dollar spent on detailing was $10.29…almost twice the return on investment in medical-journal advertising, and more than seven times the return on direct-to-consumer advertising…The first duty of doctors, at least in theory, is to their patients. Doctors must make prescribing decisions based on medical evidence and their own clinical judgements. Drug reps, in contrast, are salespeople. They swear no oaths, take care of no patients, and profess no high-minded ethical duties. Their job is to persuade doctors to prescribe drugs that are marginally effective, exorbitantly expensive, difficult to administer, or even dangerously toxic. Reps that succeed are rewarded with bonuses or commissions. Reps that fail may find themselves unemployed…A rep at the door means a delivery has arrived: takeout for the staff, trinkets for the kids, and, most indispensable, drug samples on the house…Drug reps may well have more influence on prescriptions than anyone in America other than doctors themselves…Reps can be found in hospitals, waiting rooms, and conference halls all over the country." For drug reps, "effective selling is all about developing a relationship with a doctor…'a lot of doctors just write for who they like.'…For most reps, market share is the yardstick of success. The more scripts their doctors write for their drugs, the more the reps make…Reps are pressured to 'make quota' or meet yearly sales targets, which often increase from year to year. Reps who fail to make quota must endure the indignity of having their district manager frequently accompany them on sales calls. Those who meet quota are rewarded handsomely. The most successful reps achieve minor celebrity within the company" (Elliott, 2010).

2. Drug companies now use prescription tracking, or script tracking, which aids drug reps in their choices of doctors to target. Script tracking reports can "be accompanied by a profile of a physician put together by reps…'A profile would be: 'Husband, three kids, loves needlepoint, off on Wednesdays. Amiable/ expressive, brought up suicidality four times. High writer of [drug X]. Won't accept tickets. Nurse says loves red wine, only French.'' Reps could get direct feedback on which tactics were working. If a gift or a dinner presentation did not result in more scripts, they knew to try another approach…[S]cript-tracking data [has] changed the way that reps [think] about prescriptions. The old system of monitoring prescriptions was very inexact, and the relationship between a particular doctor's prescriptions and the work of a given rep was relatively hard to measure. But with precise script-tracking reports, reps started to feel a sense of ownership about prescriptions. If their doctors started writing more prescriptions for their drugs, the credit clearly belonged to the reps. However, more precise monitoring also invited micromanagement by the reps' bosses. They began pressuring reps to concentrate on high prescribers, fill out more paperwork, and report back to management more frequently. 'Script tracking… made everyone a potentially successful rep… Reps didn't need to be nearly as resourceful and street-savvy as in the past; they just needed the script-tracking reports. The industry began hiring more and more reps, with many backgrounds in sales (rather than in, say, pharmacy, nursing, or biology)" (Elliott, 2010).

3. A 2011 study reports "…that pharmaceutical sales representatives were given access to patients' confidential medical records at physicians' offices for the purposes of trolling for prospective targets for illegal direct-to-consumer promotion of off-label uses" (Kesselheim, Mello, and Studdert, 2011).

4. "In addition to sales representatives, large companies also employ 'medical science liaisons', whose job it is to provide physicians with information without engaging in promotion, says ethics seminar leader FJ: The medical sales liaison is to the sales representative as the publication planner is to the marketer. Unlike sales representatives, medical science liaisons have advanced degrees in relevant sciences, and do not have prescription quotas they are

expected to meet. Communications between these professionals and physicians are deemed to fall under the scientific 'safe harbor', as long as they do not involve promotion" (Sismondo & Green, 2015).

*See also (Fugh-Berman and Ahari, 2007).

*Cross-reference with Gifts and meals (#6)

(17) PRACTICE-MANAGEMENT CONSULTANT

RELEVANCE:

Practice-management consultants can be hired by physicians whose practices are struggling or to improve business strategy. Practice-management consultants, often financial planners and accountants, are provided by drug companies to advise medical practices on how to run a more effective and profitable business (Elliott, 2010).

SUPPORT:

1. In a documented case, a drug company agreed to pay a practice-management consultant "a flat fee of about $50,000 to advise the clinic. But they also gave him another incentive...'We told him that if he was successful there would be more business for him in the future, and by successful, we meant a rise in prescriptions for our drugs. The consultant did an extremely thorough job. He spent eleven or twelve hours a day at the clinic for months. He talked to every employee, from the secretaries to the nurses to the doctors. He thought carefully about every aspect of the practice, from the most mundane administrative details to big-picture matters such as bill collection and financial strategy. He turned the practice into a profitable, smoothly running financial machine. And prescriptions for [the drug company] soared. When...asked...how the consultant had increased [the drug company's] market share within the clinic so dramatically, he said that the consultant never pressed the doctors directly. Instead, he talked up [the drug rep from the same company who frequently visited the office]. The consultant emphasized what a remarkable service the practice was getting, how valuable the financial advice was, how everything was going to turn around for them – all courtesy of [the drug rep]. The strategy worked... Doctors at the newly vitalized practices prescribed so many [drugs from the sponsoring company] that [the drug rep] got a $140,000 bonus. The scheme was so successful that [the drug rep] and his colleagues [at the drug company] decided to duplicate it in other practices" (Elliott, 2010).

(18) PROMOTION IN MEDICAL JOURNAL ARTICLES

RELEVANCE:

It is now widely accepted that industry-sponsored articles publish conclusions that are favorable to the sponsoring company (Perlis et al., 2005; Lundh et al., 2012; Bero et al., 2007; Dwan et al., 2008; Lexchin, 2012b; Lexchin et al., 2003; Kelly et al., 2006). Drug company-sponsored research and publications may serve as key elements in the marketing strategy for a drug (Fugh-Berman, 2010; Steinman et al., 2006).

SUPPORT:

1. Published articles may be used to obtain FDA approval for a new "on-label" indication or to "disseminate the information as widely as possible through the world's medical literature, stimulating off-label prescribing despite lack of FDA approval…The success of this strategy depend[s] on publications being favourable to [the drug]. Some employees of [drug companies] felt an obligation to publish studies with unfavourable results, and in a number of instances such results were published. However, management expressed concern that negative results could harm promotional efforts, and several documents indicate the intention to publish and publicize results only if they reflected favourably on [the drug]. As stated in the marketing assessment, 'The results of the recommended exploratory trials in [a disease category], if positive, will be publicized in medical congresses and published.' Similarly, in discussing 2 nearly identical trials that yielded conflicting results on [a drug as] monotherapy, the 'core marketing team' concluded that 'the results of [the negative trial] will not be published…Beyond publishing its own clinical trials, [drug companies expand] the literature on [drugs] by contracting with medical education companies to develop review papers, original articles, and letters to the editor about [their drugs] for $13,375 to $18,000 per article, including a $1000 honorarium for the physician or pharmacist author. For example, one 'grant request' from a medical education company to Parke-Davis proposed a series of 12 articles, each with a prespecified topic, target journal, title, and list of potential authors (to be 'chosen at the discretion of [the drug company]'). This proposal noted that 'all articles submitted will include a consistent message…with particular interest in proper dosing and titration as well as emerging [off-label] uses,' mirroring [the drug company's] promotional goals for the drug" (Steinman et al., 2006).

2. "Manufacturers sought to promote off-label drug use through journal publications...These practices included falsely reporting outcomes from patients in manufacturer-sponsored studies and publishing "ghostwritten" articles supporting an unapproved use written by the manufacturer under the name of a respected scientist" (Kesselheim, Mello, and Studdert, 2011). "Competition gives industry-backed scientists incentives to stretch the truth. 'Manuscripts have to be framed in a certain way because of the spin that the company wants"' (Elliott, 2010).

3. Companies have paid billions of dollars in fines for off-label promotion, often using company-generated research, company-paid speakers, and ghostwritten articles to imply clinical benefits in the absence of clinical trials (or the presence of negative trials); fines have also been imposed for suppressing risks or misleading clinicians about risks" (Fugh-Berman, 2013).

*Cross-reference with Stock ownership or options, bonds, and equity holdings (#22), Reprints and ePrints (#36), Off-label indications (#41)

(19) SAMPLES

RELEVANCE:

One purpose of providing free samples to prescribers is to promote off-label prescription of those medications.

SUPPORT:

1. A 2011 study found that free samples "…were intended to encourage physicians to use a product on the basis of convenience, even though it might not be approved for a certain use. In addition...free samples were intended to introduce unapproved patient populations to the manufacturer's product with the intention of stimulating their continued use" (Kesselheim, Mello, and Studdert, 2011).

2. "Accepting samples was associated with awareness, preference and rapid prescription of a new drug (Peay & Peay, 1988), and a positive attitude toward the pharmaceutical representative (Thomson, Craig & Barham, 1994)" (Wazana, 2000).

3. "Although samples are the single largest marketing expense for the drug industry, they pay handsome dividends: doctors who accept samples of a drug are far more likely to prescribe that drug later on than doctors who don't" (Elliott, 2010).

4. "The purpose of supplying drug samples is to gain entry into doctors' offices and to habituate physicians to prescribing targeted drugs. Physicians appreciate drug samples, which can be used to start therapy immediately, test tolerance to a new drug, or reduce the total cost of a prescription. Even physicians who refuse to see drug reps usually want samples (these docs are denigrated as 'sample-grabbers'). Patients like samples too; it's nice to get a little present from the doctor. Samples also double as unacknowledged gifts to pay physicians and their staff. The convenience of an in-house pharmacy increases loyalty to both the reps and the drugs they represent… Studies consistently show that samples influence prescribing choices (Chew et al., 2000; Groves, Sketris & Tett, 2003; Adair & Holmgren, 2005). Reps provide samples only of the most promoted, usually most expensive, drugs, and patients given a sample for part of a course of treatment almost always receive a prescription for the same drug" (Fugh-Berman and Ahari, 2007).

(20) SERVICE ON SCIENTIFIC ADVISORY BOARDS (SABS), CONSULTANTS MEETINGS, BOARD OF DIRECTORS, REVIEW PANELS

RELEVANCE:

The stated purpose of scientific advisory boards and consultants meetings is to obtain physician feedback on clinical trial design, educational curriculum development, and marketing strategies for medications, and there are also aspects of these meetings that suggest promotional intentions (Steinman et al., 2006).

SUPPORT:

1. "For example, attendees at one consultants meeting were invited largely because of their high rates of anticonvulsant prescribing, and sales representatives were given 'trending worksheets' to track prescribing behavior before and after the event…Some meetings resembled educational conferences, with dozens of participants and an agenda dominated by lectures from physician 'faculty'. Other meetings seemed to focus on cultivating relationships with thought leaders, as in one meeting at which lecture notes for the regional business director notified attendees that 'we would like to develop a close business relationship with you.' Participants in advisory boards and consultants meetings received honoraria in addition to paid travel, lodging, and amenities at the resorts and luxury hotels at which such events were held. In addition, a number of faculty at these events received thousands of dollars in honoraria and grants from participating in these and other [drug company] activities. These faculty may have been carefully vetted. As described by a medical education company that organized meetings, 'it is [our] policy to complete a literature search to determine who authors favorable articles on the topics outlined'. In addition, the company reserved the right in nonaccredited programs 'to probe the faculty further to definitively establish presentation content and make the appropriate changes and/or recruit an alternate speaker" (Steinman et al., 2006).

2. Drug companies employ doctors, who may also be "key opinion leaders" or "thought leaders", who can earn up to US$400 per hour, $3000 for a "scientific speech", and more than US$25,000 per year in advisory fees (Moynihan, 2005). Participants, many of whom are faculty at universities, received thousands of dollars in honoraria and grants for their participation in these drug company-run advisory boards (Steinman et al., 2006).

*Cross-reference with Consulting relationships (#3)

(21) SHORT-TERM OR LONG-TERM EMPLOYMENT AT DRUG COMPANY, SUBSIDIARY, OR SUPPORTING ENTITY

RELEVANCE:

Short-term or long-term employment refers to an individual occupying a full-time position that is potentially permanent within a drug company or supporting entity (i.e., CRO, MECC, medical writing organization (MWO)). As an employee, he/she has been trained by the company and does not simultaneously provide services for any other company and works in a company-directed schedule at a company-defined location. He/she attends in-house meetings with other company employees and receives a stable and consistent amount of remuneration (Flanagan et al., 2005).

SUPPORT:

1. Direct employment at a pharmaceutical company, subsidiary, or supporting entity. People who hold a

short-term or long-term paid position at a drug company or a drug company subsidiary have, or have had, an interest in the financial success of their employer(s). At large drug companies, especially employees in "…management positions earn significant bonuses in cash and stock options. At many biotech companies, all employees receive stock options, which, if the company does well, can be lucrative" (WetFeet, 2012).

*Cross-reference with Stock ownership or options, bonds, and equity holdings (#22)

(22) STOCK OWNERSHIP OR OPTIONS, BONDS, AND EQUITY HOLDINGS

RELEVANCE:

Stock ownership, options, bonds, and equity are forms of financial interest that may be given to employees to provide them with a stake in a company's success.

SUPPORT:

1. The provision of corporate stock options to both executive and non-executive employees in the pharmaceutical industry is common. For example, researchers who dictate how drugs should be prescribed may have extensive financial ties, including stock ownership or options, bonds, and equity holdings, with the pharmaceutical industry. Firms tend to use greater stock option compensation to attract and retain certain types of employees and to create incentives to increase firm value. Providing researchers who publish articles on prescribing choices with these financial incentives is a direct financial conflict of interest because their published recommendations and expert opinions have a direct effect on sales and, therefore, the price of the stocks that they are receiving (Core and Guay, 2001; Taylor and Giles, 2005; Bekelman, Li, and Gross, 2003).

2. Financial interest in companies may reasonably appear to affect and be affected by research. "Such interests include stock and stock options totaling more than $10,000" (Lo, Wolf, and Berkeley, 2000).

*Cross-reference with Promotion in medical journal articles (#18), Short-term or long-term employment at drug company, subsidiary, or supporting entity (#21)

(23) TRANSPARENCY OF FINANCIAL CONFLICT OF INTEREST DISCLOSURES

RELEVANCE:

Transparency focuses on not only the degree to which disclosures are required, but also whether they are made publicly available by peer-reviewed academic medical journals once they are disclosed.

SUPPORT:

1. It is generally agreed upon that financial ties and conflict of interest relationships should be disclosed when publishing articles in academic peer-reviewed medical journals (Mendelson et al., 2011). However, disclosure alone is only a first step toward protecting the integrity of academic medical publishing. While there is a recent trend toward increased disclosure (Mendelson et al., 2011), transparency and public availability of disclosures must also be ensured, as studies have found that authors' disclosures are often missing or inconsistent across their published medical (Langer et al., 2012; Cosgrove and Krimsky, 2012; Cosgrove et al., 2009; Norris et al., 2013; Neuman et al., 2011; Papanikolaou et al., 2001; Brix Bindslev et al., 2013; Weinfurt et al., 2008). When information is available, a large percentage of authors often disclose financial conflicts of interest (Langer et al., 2012).

2. "Over the past 25 years, it has become standard practice in medical journals to require authors to disclose relationships with industry (Institute of Medicine, 2009; International Committee of Medical Journal Editors, 1993; Relman, 1984). However, the requirements vary across journals and often lack specificity. It is left to authors to determine the appropriate period for disclosure or the relevance of a financial relationship to a submitted article. As a result, disclosures may be inconsistent, with neither reviewers nor readers fully informed of the ties between authors and industry (Weinfurt et al., 2008)… Findings indicate that current journal disclosure policies do not yield complete or consistent information regarding industry payments" (Chimonas, Frosch, and Rothman, 2010).

3. "Authors of original articles, reviews, and editorials that appear in academic journals should be required to disclose to journal editors all financial arrangements with private firms within the past three years, whether or not those arrangements are directly related to the subject of the article…Journal editors should amend their disclosure policies to include all conflicts of interest that are in any way related to articles submitted for publication. Standards that require 'relevance' or 'direct relevance' for a conflict to be disclosed provide a loophole for many researchers who do not with their relationships with companies be revealed" (Goozner, 2004).

CATEGORY B: ROLES IN THE RESEARCH, WRITING, AND PUBLICATION PROCESSES

(24) ACKNOWLEDGE-MENTS, "EDITORIAL ASSISTANCE", "WRITING SUPPORT", OR "WRITING ASSISTANCE"

RELEVANCE:

Individuals may be thanked for "editorial assistance", "writing assistance", or "writing support" in the acknowledgements sections of published manuscripts. Researchers have found that this typically implies that medical writers, or ghostwriters, wrote the manuscript and the named authors on the published paper are guest authors (Elliott, 2010; Healy and Cattell, 2003; Leo, Lacasse,

and Cimino, 2011; Fugh-Berman, 2013).

SUPPORT:

1. "Perhaps the most pernicious practice in ghostwriting involves thanking writers for providing 'editorial assistance' in the acknowledgements section of the paper instead of the authorship byline, which essentially changes the rule of authorship attribution so that ghostwriting is acceptable. Several groups in medicine including the European Medical Writers Association (EMWA) sanction this practice. While the average reader likely interprets 'editorial assistance' as help with grammar or improvements to the overall readability of the article, in reality, such 'assistants' make major contributions to papers, and would commonsensically be considered co-authors. Tellingly, many medical writers are 'editorial assistants' on some scientific papers, but co-authors on others. It would seem obvious that someone employed as a 'medical writer' would be an author, but current dialogue on ghostwriting ignores such common-sense interpret-ations" (Leo, Lacasse, and Cimino, 2011).

2. "Listing ghost authors as editorial assistants allows pharmaceutical companies to publish articles with conflicts-of-interest that are not transparently reported. Editorial assistants are not mentioned in the abstract, are not indexed in publication databases, are not mentioned in subsequent citations, and are never mentioned in news media accounts of the article. In other words, the fact that a pharmaceutical company directly co-authored the paper is concealed from view. That this is seen as acceptable in an era of increased disclosure of conflicts-of-interest is puzzling" (Leo, Lacasse, and Cimino, 2011).

3. Editorial assistance is "often an industry code word for ghostwriting" (Fugh-Berman, 2013) and "[…] may be so widespread that it is considered normal. This could explain why several authors of ghostwritten articles have defended their involvement" (Fugh-Berman, 2010).

4. "[A]s Senator Grassley pointed out in his letter to Wyeth, the final journal publications only acknowledged the medical writers for the 'editorial assistance' or 'assistance.' The articles did not disclose that Wyeth had initiated and paid DesignWrite for the development of the manuscripts and that the medical writers were hired and compensated by DesignWrite. Wyeth stated that DesignWrite was compensated for its work in getting manuscripts drafted and submitted for publication but payments were not allocated for individual articles" (United States Committee on Finance, 2010).

5. "The first author on the [Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effective-ness (ADVANTAGE) seeding] trial report said that Merck came to him after the study was completed and asked him to help with the editing. He was paid, which is highly unusual for a first author of a trial report, and the report was already written up by Merck; a Merck employee was thanked for 'assistance with manuscript preparation' (Lisse et al., 2003)" (Gotzsche, 2013).

*Cross-reference with Guest authors or honorary authors (#28), Medical writers, medical ghostwriters, or ghost authors (#33)

(25) CREATORS OF TRIAL DESIGNS AND PROTOCOLS

RELEVANCE:

The people who design clinical trials and their protocols may be company employees who may have incentive to design the trials and the involvement of investigators in a way that is favourable to the sponsoring company.

SUPPORT:

1. "In some multicenter trials, authors may not even have access to all their own data. The Pharmaceutical Research and Manufacturers of America, the trade association of the industry, justified withholding data in this way: 'As owners of the study database, sponsors have discretion to determine who will have access to the database.' At its extreme, investigators have become little more than hired hands, supplying patients and collecting data according to the company protocol" (Angell, 2008). Company employees who design clinical trials and their protocols are commonly unacknowledged contributors to published articles (Sismondo, 2007).

(26) GHOST MANAGEMENT

RELEVANCE:

Ghost management is an academic analysis of the process by which medical journal articles may be ushered through a careful process of production, revision, and shaping to contribute to a larger promotional narrative about a drug or disease state that can be treated by a drug manufactured by the sponsoring company.

SUPPORT:

1. Ghost management of medical research and publishing occurs "when pharmaceutical companies and their agents control or shape multiple steps in the research, analysis, writing, and publication of articles. Such articles are 'ghostly' because signs of their actual production are largely invisible – academic authors whose names appear at the tops of ghost-managed articles give corporate research the appearance of independence and credibility. They are 'managed' because those companies shape the eventual message conveyed by the article or by a suite of articles…A substantial percentage of medical journal articles…are ghost managed, allowing the pharmaceutical industry considerable influence on medical research, and making that research a vehicle for marketing" (Sismondo, 2007).

2. "We apply the term ghost management when pharmaceutical companies and their agents control or shape several crucial steps in the research, writing, and publication of articles… Companies aim to maximize the number of publications from positive trials, minimize those from negative trials, and ensure that the results of the study are published promptly and in prominent journals (Melander et al., 2003). Ghost management makes apparently scientific

research a marketing tool" (Sismondo and Doucet, 2010).

3. Ghost managed articles are common in the published medical literature and "amounts to thousands of articles per year – publications plans for 'blockbuster' drugs (one with annual sales of US$1 billion or more) can involve 80 to 100 articles appearing in reputable medical journals over the course of a few years…In the ghost management of knowledge, and its dissemination through KOLs, we see the pharmaceutical industry going to great lengths to hide or disguise the interests behind its research and education" (Sismondo, 2011).

4. "On the basis of the data they produce, as well as publicly available medical research, pharmaceutical companies and their agents produce substantial numbers of scientific manuscripts on major current drugs. They recruit academic researchers to serve as the listed authors of those manuscripts; those authors' contributions typically range from having supplied some of the patients for a clinical trial, to editing the manuscript, to simply signing off on the final draft. The companies submit the manuscripts to medical journals, where they generally get published, contributing to received scientific opinion. Marketing departments of the companies involved often buy thousands of reprints from the journals, so that their sales representatives can present to physicians supposedly independent scientific evidence of the safety and efficacy of the drugs in their portfolios. Roughly 40% of the sizeable medical research and literature on recently approved drugs is 'ghost managed' in the above way by the pharmaceutical industry and its agents (Sismondo, 2007)" (Sismondo, 2011).

5. "Ghost management of medical journal publications is clearly a substantial business, employing thousands of marketers, writers, and managers. It is large enough that the industry has established the International Publication Planning Association. This organization, which appears to be dominated by pharmaceutical companies, organizes meetings, keeps a directory of experts, and gives awards to honor planners (The International Publication Planning Association, 2006). In addition, the International Society for Medical Publication Professionals also organizes meetings, has committees to develop policy, and posts job advertisements (International Society for Medical Publication Professionals, 2006). Both of these associations compete with for-profit companies offering similar services, such as the Center for Business Intelligence, which held forums for Strategic Publication Planning in 2005 and 2006 (Center for Business Intelligence, 2006)" (Sismondo, 2007).

*Cross-reference with Publication planning (#35)

(27) STATISTICIANS

RELEVANCE:

Statisticians on clinical papers may be employed by either the sponsoring pharmaceu-tical company (Sismondo, 2007) or the CROs (Wager, 2011) to which the pharmaceutical companies outsource their research.

SUPPORT:

1. Drug company statisticians are commonly unacknowledged contributors to published articles (Gotzsche et al., 2007).

2. "In the paper by Gotzsche and colleagues (2007) the high prevalence of ghost statisticians was particularly troubling. If no one named on a paper was actually responsible for the analysis, which was instead done by a shadowy group of unnamed individuals, then it is hard to have any confidence in the findings overall" (Barbour, 2010).

3. "We take issue with this widespread practice of not including statisticians as authors for reports of randomised trials…the statistical report is a fundamental part of the research that has a crucial influence on what is written in the publication. Omission of a company statistician, usually also from the acknowledgement section, deprives readers of a key insight into the role of the company, although it is sometimes evidence that reports of industry-sponsored trials contain sophisticated statistical analyses that are beyond the capabilities of the authors (Senn, 2002). We cannot exclude the possibility that data analyses in some of the trials, and corresponding sections in protocols, were performed by company employees who were named authors but not statisticians, but it is unlikely since the pharmaceutical corporations usually have strong departments of statistics (Senn, 2002)" (Gotzsche et al., 2007).

4. "Execution of the study according to plan and objective depiction of the results can also be influenced, e.g., by contractual stipulations that grant the pharmaceutical company access to the trial data or give it the power to prevent the publication of results. Moreover, the presentation of results can be manipulated by ghostwriters and guest authors…This includes statisticians who analyze the results" (Schott et al., 2010).

(28) GUEST AUTHORS OR HONORARY AUTHORS

RELEVANCE:

Guest authors, sometimes referred to as honorary authors, tend to be prominent physicians or researchers who are recruited by MWOs or drug companies to sign onto papers as authors, despite that they neither conducted the study, nor wrote the manuscript (Unknown, 2006). Case studies of internal industry documents in the Drug Industry Documents Archive (DIDA) exemplify that the practice of inappropriate authorship attribution is common (Ross et al., 2008). In academia it is common for senior researchers and department chairs to be honorary authors on publications completed by their own research teams (Support #1 below); however, the type of honorary authorship with which this glossary is concerned is associated with industry originated manuscripts and the practice of medical

ghostwriting (Support #2-6 below).

SUPPORT:

1. Honorary, or gift, authorship is a term that has been used when "[i]n some academic units, for example, junior scholars are expected to list their department chairs or lab chiefs as coauthors on all their publications, whether or not these people have actually contributed anything to the paper...Some senior academics argue that they should be listed as coauthors on anything that is written by anyone being paid out of their grants." This practice is "…typically frowned upon by journal editors but that remains relatively common. A more benign version of honorary authorship is when a senior academic lists a junior partner (such as a graduate student or research assistant) as a coauthor on a publication out of generosity, even though that person has contributed very little. As a result, it can be difficult to look at the list of authors on a research paper and decode exactly who did what. An author may be the head of the department where the article was produced, or the person who wrote the grant that funded it, or simply a powerful senior physician to whom a junior academic has offered authorship in order to curry a favor" (Elliott, 2010).

2. "A particularly pernicious kind of honorary authorship occurs when distinguished academic researchers are listed as the authors of papers ghostwritten by industry. In these cases, the sham academic author is used to hide conflicts of interest and to give the resulting paper the appearance of impartiality. This is what I call deceptive honorary authorship (as opposed to nondeceptive honorary authorship, in which there are no ghostwriters or undisclosed conflicts of interest). These labels highlight the difference in motivations underlying each type of honorary authorship. Deceptive honorary authorship occurs when honorary authors put their names on papers to intentionally mislead the scientific community and public about who funded and performed the research. In this context, deceptive honorary authorship is part of a deliberate attempt to manipulate the biomedical literature for financial gain. Sponsoring companies place favorable articles promoting their marketing messages in well-respected scientific journals under the names of well-respected academic scientists to increase the effectiveness of their marketing by making it seem impartial when, in fact, it is not. Since doctors use these articles to guide their prescribing practices, this kind of honorary authorship leads to increased sales, as doctors are impressed by the prestige of the sham author and the seemingly impartial results. In addition, the honorary author also benefits, usually by an honorarium and by being able to use the publication credit towards professional advancement… The honorary author is guilty of academic dishonesty (i.e., plagiarism) in taking academic credit for another's work. Additionally, the honorary author deliberately conceals underlying conflicts of interest. Ghostwritten articles necessarily conceal conflicts of interest because transparency makes a paper not ghostwritten. The end result of this behavior is that the deceptive honorary author undermines the system of scientific communication in a way that has the potential to seriously harm people. Industry groups rely on ghostwritten articles to give their preferred messages the appearance of impartiality. This deception directly influences the treatment provided by medical professionals mislead by the deliberate manipulation of the scientific literature which can lead to real harm. Deceptive honorary authors' complicity in an elaborate scheme of scientific deception makes them guilty of serious breach of research ethics…The potential for harm due to the manipulation of a scientific literature is high. Recent documents revealed in court cases surrounding the drug rofecoxib (sold under the brand name Vioxx by Merck) suggest that significant portions of the biomedical literature relating to the safety and efficacy of pharmaceutical products are written by third-party scientific communications companies contracted by pharmaceutical companies and published under the names of academic authors who did not write the papers in question" (Moffatt, 2011).

3. After an article, written by a ghostwriter or medical writer, is approved by the sponsoring company or MECC, the guest author, who was recruited to sign his or her name to the pre-crafted manuscript, "submits the manuscript as his or her original work to a journal specified by the pharmaceutical company. If the journal asks for revisions or clarifications, the medical writer writes the response, again for the guest author's signature" (Fugh-Berman and Dodgson 2008). Some guest authors "…take an active role in the process and make changes at the outline and manuscript stages, but at every stage, the manuscript is monitored by the agency and the pharma company to ensure it remains on-message. After pharma sign-off, the 'author' is generally asked to submit to the journal directly to minimize the appearance of pharma involvement, and then receives an 'honorarium'. Increasingly, companies no longer pay 'authors' directly, but reward them intermittently for their interest by providing 'research grants'" (Matheson, 2008).

4. "Many authors on ghost-managed manuscripts are medical specialists…[and] have established relationships with [the sponsoring pharmaceutical company]. They are typically faculty in medical schools, generously called 'thought leaders,' 'key opinion leaders,' or more normally 'KOLs'. Publication planners make KOLs their authors on articles, and their speakers at conferences, workshops, and other events. In so doing, they build reputations, turning people into opinion leaders who are even more 'key.' Because medical schools place unrealistic expectations on their researchers, academic KOLs are keen to add to their CVs; it is not unheard of for researchers to list a thousand authored and coauthored scientific publications. Most medical science articles have multiple authors, so researchers are used to making modest contributions to published research. Publication planners further pare down the necessary work. To some KOLs, a free manuscript may feel like another perk of having good relations with a drug company, complementing the dinners, the trips to meetings and conferences, speaking and consulting fees. In some cases, academic authors may not even be fully aware, or may decide not to be aware, that they are freeloading off a

drug company…Among themselves, planners portray authors as lazy, greedy, and prone to miss deadlines. For the sake of legitimacy, planners would like authors to make some contribution to manuscripts. However, they need to be coaxed and coached" (Sismondo, 2011).

5. "Authors, it seems, are largely interchangeable. They were all 'to be determined' until the publication team thought that the manuscript was nearly ready to be sent out to a journal. At that point, Wyeth appears to have determined who the authors would be, and contacting them was added to its 'to do' list. Perhaps there was not much consultation even then. When [an author] established ties with Organon [a medical writing organization], [the drug company] no longer wanted to work with her and simply replaced her with two other authors. It is not clear that she was ever notified that she had been put on or taken off the author list" (Sismondo, 2011).

6. "Guest authors and KOLs more generally are part of a largely successful attempt to disguise conflicts of interest and the biases they create" (Sismondo, 2011).

*Cross-reference with Honoraria and payments (#8), Acknowledgements, "editorial assistance", "writing support", or "writing assistance" (#24), Medical writers, medical ghostwriters, or ghost authors (#33)

(29) INDUSTRY OBSERVERS

RELEVANCE:

Observers may be drug company employees who may attend study committee meetings and ascertain the use of company data in order to ensure that their company's data is being interpreted favourably in comparison to competitor products' data.

SUPPORT:

1. "Observers…are not uncommon. The idea is that they are invited to see at first hand what is going on and to sit in at study committee meetings, but not usually to contribute or have a vote. You get observers of this sort in many areas, not just science. The issue in this setting…is that private data from many companies' trials are being pooled for meta-analysis. Companies are increasingly allowing this but they remain very scared that their data will be analyzed to show weaknesses in the products. So they need all sorts of guarantees that head-to-head comparisons of rival drugs will not be carried out etc. I expect the inclusion of observers [in this case] is primarily to assuage the concerns of pharma…it is likely their presence would only be possible with, and in turn would reinforce, an industry-friendly culture and climate within the research group" (Personal communication, 2015).

(30) INVOLVEMENT OF A MEDICAL WRITING ORGANIZATION (MWO) OR MEDICAL COMMUNICATIONS COMPANY (MCC)

RELEVANCE:

The term medical writing organization (MWO) is sometimes used synonymously with Medical Education Communications Company (MECC), Medical Communications Company (MCC), and Medical Publications Company. These organizations can be contracted to work independently from, or with, each other to write manuscripts with embedded promotional messages. The manuscripts are later signed by recruited guest authors.

SUPPORT:

1. Drug companies have contracted with "medical publishing companies to have manuscripts prepared." These companies sometimes describe themselves as "a full service medical publishing group specializing in the development of scientific literature and other resource media with a direct application to clinical therapeutics" and some of these companies have been "'serving members of the pharmaceutical industry and medical associations since 1985' [or] 'a full-service health marketing communications company committed to the highest quality of service…We're there pre-launch, preparing the market for a product's introduction. At launch, we establish the foundation for product uptake.' Documents were found demonstrating that medical publishing companies provided near complete drafts of review manuscripts to authors for editing, in addition to managing submissions and revisions'" (Ross et al., 2008). Documents have been "…found describing [drug company] employees contracting with medical publishing companies to ghostwrite review manuscripts focused on [a drug] and subsequently recruiting external, academic affiliated investigators to be guest authors" (Ross et al., 2008). Documents also show that these publishing companies provide updates on the "development and estimated delivery dates for [a number of] manuscripts related to [a drug] that the company was preparing, including intended titles, authors, and journals" (Ross et al., 2008). "Documents also were found demonstrating that medical publishing companies played critical roles in overseeing the development, organization, and manuscript drafting of supplemental issues focused on [the drug] for journals" (Ross et al., 2008). These companies also "…manage article submissions to meetings, and as samples of its service it provides hypothetical lists of abstracts and presentations, with their status, dates of presentation, etc." (Sismondo, 2007).

2. Internal industry documents show that "[p]rimary publications (articles that report clinical trials) ghostwritten by [a MWO] included four manuscripts on [trials of a drug] for which [the MWO] paid US$25,000 each. Secondary publications (articles that follow clinical trial reports and contain 'subsequent analyses and reviews of the drug and its field use') included 20 review articles that [the MWO] was assigned to write in 1997 for $20,000 each, a price that later rose to $25,000. Abstract production cost $4,000. [The MWO] charged $10,000 for editing manuscripts and $2,000 for editing abstracts 'written by author or other agency'. As part of its publication planning, [a drug company's] Marketing Department convened monthly meetings to discuss publication strategies, draft outlines, and sometimes adjust the overall

publication plan. In 2002, for example, [a drug company's] management 'charged the Publication Committee with increasing the number of positive [drug]-related publications'" at the rate of 1 publication per month (Fugh-Berman, 2010).

3. "In addition to the publication planners, a much higher number of medical writing companies and individual writers create articles and presentations without engaging in broader publication planning; these may be adjuncts to publication planners. To provide an indication of the scale, the American Medical Writers Association boasts a membership of more than 5,000 (American Medical Writers Association, 2007a); judging from the organization's officers and the content of its conferences, it appears to be dominated by MECCs (American Medical Writers Association, 2007b; American Medical Writers Association, 2007c)" (Sismondo, 2007).

4. Internal industry documents have shown that employees from medical publication companies or medical writing organizations "…manag[e] submissions and revisions. For instance, in preparing one manuscript, [the medical publications company] indicate[d] in a publications status report that the first draft was sent to [the drug company] and the [publications] company was awaiting comments, but an author needed to be invited. In another e-mail that discusses an article with which the company was involved, a [publications company] representative states: 'The .1439 journal article that was submitted to Pharmacotherapy by Dr. William Garnett has been accepted (I believe) with revisions. He has faxed me only the reviewers' comments, but is mailing me the entire packet that they sent to him. He would like us to make the revisions, as he is too busy at the moment to make them himself. According to the proposal (Doc #66468) there is no mention of whether revisions are included, or can be done for an additional fee" (Ross et al., 2008).

5. An important role of MWOs or publications companies is "…to manage 'authors' and journals…[A MWO's] ghostwriters also managed journals by responding to the editor and reviewer comments. Ghostwriters argued for retention of specific marketing messages, sometimes scolding reviewers under the guise of defending peer-review. Responses to one presumably unfavourable review included: 'The review of the current paper is not the appropriate place to criticize methodologic flaws of published papers'; and 'The reviewer's suggestion to revise the statement on page 8…is not justified. This interpretation is well documented.' In one case, a ghostwriter asked the author for assistance in preparing a response: '…If you have any thoughts about how we might reply to this reviewer's comment, please let us know'" (Fugh-Berman, 2010).

*Cross-reference with Involvement of a contract research organization (CRO) or site-management organization (SMO) (#31), Involvement of a medical education communication company (MECC) medical communications company (MCC), medical education company (MEC), or medical education service supplier (MESS) (#32), Publication planning (#35)

(31) INVOLVEMENT OF A CONTRACT RESEARCH ORGANIZATION (CRO) OR SITE-MANAGEMENT ORGANIZATION (SMO)

RELEVANCE:

Contract research organizations and site-management organizations are for-profit research companies that may be contracted by drug companies to conduct a clinical trial, collect, analyze, and interpret the data (Fisher, 2008).

SUPPORT:

1. The commercial-research enterprise has grown and "[t]he largest of the new businesses are called contract research organizations" and include companies worldwide. CROs are "…hired to shepherd a product through every aspect of its development, from subject recruitment and testing through FDA approval. Speed is critical: a patent last twenty years, and a drug company's aim is to get the drug on the shelves as early in the life of the patent as possible" (Elliott, 2010). "Of industry funding, 70% goes to CROs that neither make ownership claims on data nor expect to publish the data themselves: CROs perform research to order. By its nature, CRO research tends to be ghostly. The 30% of industry funding that goes to academic researchers often also comes with strings attached that can allow sponsors to prepare drafts, edit drafts, delay publication, prevent full access to data, and so on – in short, creating conditions that allow for ghost management" (Sismondo, 2007).

2. Most researchers have little to say in research design, since the majority of the industry's spending on clinical trials goes to CROs [contract research organizations], and even academic researchers are heavily influenced by sponsors' designs and requests (Abraham, 2005)" (Sismondo, 2008a).

3. "Conflicts of interests may trouble academics, but they do not seem to present obstacles for CROs. Once CROs entered the arena, AHCs [academic health centers] could no longer engage in older vintages of 'open science'. According to some estimates, one-third to one-half of the clinical trial contracts in the 1990s with AHCs...contained restraint clauses, confidentiality provisions, publication embargoes, and a host of other legal controls over proprietary information" (Mirowski and Van Horne, 2005).

4. "CROs participate in an altogether different kind of economy, in which various claims about drugs are being 'sold' to regulators, doctors writing prescriptions, and increasingly, to the patient end-user. Should these claims of efficacy be challenged, they could then potentially be litigated in a court of law and negotiated in terms of monetary liability of a corporate entity. The 'responsibility' in question [is] that of a commercial corporation to its shareholders, the regulators, and (to a lesser extent) its customers...Especially for the CRO, there exists no single person or small number of people whose probity stands planted firmly behind the information disseminated

(after all, mostly they are merely employees; many have moved on even before the project was completed; and corporate officers are not personally liable for product negligence); there are only the contractual obligations of the corporations...The scribe who puts her pen to paper is just one more employee, enjoying the same social obligations and dispensations as the laboratory technician (with probably commensurate job security)" (Mirowski and Van Horne, 2005).

5. "Commercially oriented networks of contract-research organizations (CROs) and site-management organizations (SMOs) have altered the drug-trial landscape, forcing academic medical centers to rethink their participation in industry-funded drug research…CROs may subcontract with for-profit SMOs [site management organizations] to organize networks of community physicians, ensure rapid enrollment of patients, and deliver case-report forms to the CRO...Companies may design studies likely to favor their products [using strategies like testing the sponsor's drug] in a healthier population…with an insufficient dose…[using] surrogate end points that may not correlate with more important clinical end points" (Bodenheimer, 2000).

6. "…[T]rials conducted in the commercial sector are heavily tipped toward industry interests, since for-profit CROs and SMOs, contracting with industry in a competitive market, will fail if they offend their funding sources" (Bodenheimer, 2000).

*Cross-reference with Involvement of a medical writing organization (MWO) or medical communications company (#30), Involvement of a medical education communication company (MECC) medical communications company (MCC), medical education company (MEC), or medical education service supplier (MESS) (#32), Publication planning (#35)

(32) INVOLVEMENT OF A MEDICAL EDUCATION COMMUNICATION COMPANY (MECC), MEDICAL EDUCATION COMPANY (MEC), OR MEDICAL EDUCATION SERVICE SUPPLIER (MESS)

RELEVANCE:

Medical education communication companies (MECCs), or medical education service suppliers (MESSs), sometimes referred to as medical communications companies (MCCs), are among the most significant but least analyzed health care stakeholders. Supported mainly by drug and device companies, they are vendors of information to physicians and consumers and sources of information for industry (Rothman et al., 2013). These companies usually compete for contracts for specific drugs (Matheson, 2008).

SUPPORT:

1. "Some conflicts of interest are invisible. Pharmaceutical companies routinely seed medical literature with reviews or commentaries that advantageously frame a marketed drug, but some sponsored articles never mention the targeted drug. Both types of articles are usually written by a medical education company (MEC) that receives funding from a pharmaceutical company… The arrangements made between drug companies or MECs and physicians are often discreet; negotiations are done over the phone, or in telegraphic e-mails. Paper trails are minimized; there are no invoices, no contracts, and no written scope of work. Payments may not be traceable to services rendered, or to the sponsoring pharmaceutical company" (Fugh-Berman, 2005).

2. Companies can hire one or multiple MECCs to work on the promotion of one drug (Sismondo, 2011). "Between 1998 and 2006, commercial support for CME increased by a fourfold margin to a total of $1.2 billion. By 2006, over 60 percent of CME was funded by commercial sources. During this same period, profit margins for accredited CME providers increased nearly sixfold, from 5.5 percent to 31 percent, with total income reaching $2.38 billion" (Elliott, 2010). "Unsurprisingly, MECCs advertise their ability to do 'promotion through education' and that CME can be 'custom tailored to meet the pharmaceutical marketers' needs'" (Sismondo, 2011).

3."Pharmaceutical companies also have a presence in continuing medical education (CME), required of most physicians in North America in order to maintain their accreditation. More than 60% of all support for CME comes from pharmaceutical and medical device companies (Steinbrook, 2008). The MECCs that organize the courses are legally allowed to provide organization, pay for speakers, help speakers prepare for their talks, and provide entertainment for participants. The companies do not control the content of CMEs, but if they have chosen their speakers well, supported those speakers' research, and given speakers templates and slides for their talks, these courses will convey preferred messages (Elliott, 2004; Steinman & Baron, 2007). An industry education specialist says that the idea is 'control – leaving nothing to chance' (Bohdanowicz, 2009). This is the best kind of marketing, directed at audiences needing to educate themselves, and provided by sources that the audiences have reasons to trust. Unsurprisingly, MECCs advertise their ability to do 'promotion through education' (Research and Markets, 2001) and that CMEs can be 'custom tailored to meet pharmaceutical marketers' needs' (MD NetGuide, 2004)" (Sismondo, 2011).

4. "Known best for arranging continuing medical education (CME) programs, they also may develop prelaunch and branding campaigns and produce digital and print publications...[MCCs promote] online CME courses as a convenient and cost-free alternative to live CME courses...To enrol in the CME course, physicians had to provide personal information, such as name, e-mail address, specialty, and license number. How MCCs might use the personal data and track physician web activity was described in the Privacy Policies sections of their websites." Some MCCs use tools such as "cookies" and web "beacons" and share personal information with

third parties, including "unnamed third parties" and "companies with which they worked or might merge." A 2013 study found that "among the 14 companies that released data in 2010, MCCs received an aggregate of $170 million, more funds than any other recipient, including academic medical centers, professional associations, and research organizations. The top 5%, almost all for-profit companies, received 59% of the funds. Absent industry disclosures, none of this information would have become publicly available... Medical communication companies receive substantial support from industry, and the majority are for-profit, conduct CME programs, track website behavior, and may share information with third parties" (Rothman et al., 2013).

5. MECCs are also hired to organize teleconferences, coordinate advisory boards and consultants meetings, and conduct tactical planning to promote drugs. When drug companies hire MECCs for this many purposes, they have "incentive to develop educational programs that are consistent with the marketing goals and to control content in a way that reflected favorably on the sponsor. For example, in 1996, one medical education company prepared a marketing proposal for [its drug company sponsor] outlining 24 tactics to increase [prescriptions of a drug] shortly after using an unrestricted grant from the drug company to organize a series of study programs on the use of [related medications]. Although the educational program prepared by this company was accredited by ACCME, [drug company] representatives were invited to a curricular development meeting, recruited physicians to participate in the course, and followed attendance counts at each program meeting" (Steinman et al., 2006). "In another case, another medical education company that organized consultants meetings for [the drug company] received a grant to assemble and train speakers to deliver grand rounds lectures on [a class of drugs for a specific disease state] at approximately 70 community and teaching hospitals across the northeastern United States. [The drug company] also sought to provide unrestricted educational grants to locally organized symposia at which it expected [its drug] to be favourably discussed" (Steinman et al., 2006).

6. MECCs also offer substantial assistance in the development of manuscripts including assisting the author with "identifying and collecting…appropriate cases, analyzing data, writing a manuscript, or whatever [the author] needs" (Steinman et al., 2006).

7. "Many pharmaceutical companies use medical education communication companies (MECCs) to recruit academic physicians and scientists to "author" publications crafted by industry. Articles may be ghostwritten by a medical writer. Authors who actually write their own articles may still submit to "ghost-management", allowing a company to provide statistical analysis or "editorial assistance" (often an industry code word for ghostwriting), either of which provides a company the opportunity to insert marketing messages into an article. Ghostwriting has been used to promote Zyprexa (olanzapine), Paxil (paroxetine) "Fen-phen" (fenfluramine and phentermine, used for weight loss), Vioxx (rofecoxib, an analgesic), and Zoloft (sertraline, an antidepressant). Undoubtedly, many other drugs are promoted by ghostwriting... The extent to which basic scientists participate in ghostwritten articles is unknown...Even if a researcher does not allow a sponsor to ghostwrite an article, industry review of articles by a sponsor may result in the insertion of subtle marketing messages that researchers may not recognize as advertisements" (Fugh-Berman, 2013).

8. Drug companies have "'…turned to the medical education and communication companies (MECCs) DesignWrite, Parthenon Publishing, and Oxford Clinical Communications to work on publication plans and publications for [drugs]. These agencies created suites of articles and conference presentations that were intended to maintain and expand the market for drugs like [X, Y], and related products. Over the course of 6 years, DesignWrite produced for [a drug company] 'over 50 peer-reviewed publications, more than 50 scientific abstracts and posters, journal supplements, internal white papers, slide kits, and symposia' (DesignWrite, 2005)" (Sismondo, 2011).

*Cross-reference with Involvement of a medical writing organization (MWO) or medical communications company (#30), Involvement of a contract research organization (CRO) or site-management organization (SMO) (#31).

(33) MEDICAL WRITERS, MEDICAL GHOSTWRITERS, OR GHOST AUTHORS

RELEVANCE:

Medical writers are also commonly known as "ghostwriters" or "ghost authors". The use of medical writers and, therefore, the practice of ghostwriting, is so prevalent that there now exist medical writers associations that provide resources to medical writers. In the United States, this association is called American Medical Writers Association (AMWA) (American Medical Writers Association [AMWA], 2015) and the AMWA-Canada (AMWA, 2009) is the Canadian chapter of this association. The comparable association in Europe is called the European Medical Writers Association (EMWA) (European Medical Writers Association [EMWA], 2015).

SUPPORT:

1. Medical ghostwriting is "the practice through which researchers agree to put their names on texts that had been composed by unnamed third parties, who held final control over the content of the manuscript" (Mirowski and Van Horne, 2005). In ghostly papers, "[a]uthors, it seems, are largely interchangeable. They were all "to be determined" until the publication team thought that the manuscript was nearly ready to be send out to a journal. At that point, [the drug company] appears to have determined who the authors would be, and contacting them was added to its 'to do' list…Even before their authors are chosen, drug

company articles run a gauntlet of reviews by planners and company scientists and are vetted and revised many times. Those articles have been given much more thorough reviews than medical journals can ever give. Authors have little to add other than their names, and by adding their names they gain prestigious publications, which are the basic measure of worth in academic settings" (Sismondo, 2011).

2. "Medical writers, who are often scientists or health professionals, are crucial to publication planning. They ensure that manuscripts are scientifically correct, professional, organized, readable, persuasive, and submitted on time. Medical writers prepare primary and secondary publications, including clinical trial reports and reviews; they may also prepare meeting materials and abstracts. They may work directly for pharmaceutical companies, most often as freelancers, or they may be employed by medical education communications companies (MECCs), which derive most of their income from pharmaceutical companies. A pharmaceutical company may create a publication plan internally or work with a MECC on the plan...Potential guest authors may also be listed. Once the topic of an article is chosen, a medical writer generates an outline, which is approved by the sponsoring pharmaceu-tical company. The writer then researches and writes the paper, incorpor-ating the appropriate marketing message; an experienced writer may be able to communicate messages that align with a sponsor's marketing objectives even when specific messages are not provided. After the completed article is approved, the guest author, usually an academically affiliated physician, is approached by the sponsor. Guest authors (who may receive payment through a MECC) are generally offered the option to contribute to or amend the article; they usually realize that edits disadvantageous to a sponsoring company's marketing goals will result in the article not being published – or being published under another physician's name" (Fugh-Berman and Dodgson, 2008).

3. Medical writers may perceive their role to be noble in ensuring that research is reported responsibly (Wager, 2011). Medical writers are typically paid $90 to $120 per hour and the average freelance medical writer in the United States can make $120,000 to $150,000 or more per year, depending on level of education and experience. Each manuscript usually costs the sponsor between $1,000 and $2,500 (Fugh-Berman and Dodgson, 2008); and publishing a paper in a high-impact medical journal could net the ghostwriter payment of approximately US$20,000 (Mirowski and Van Horne, 2005).

4. "Some medical writers distinguish between ghost authoring and ghostwriting. 'Ghost authoring is 'We write it, you sign it'", while "[g]hostwriting...is closer to a kind of joint authorship, where a writer collaborates with an author but without receiving any formal acknowledgement. This practice is more controversial. Critics of ghostwriting say the lack of acknowledgement is an effort to hide the involvement of industry and make it appear as if the article has originated from a university. Defenders say that often the writer simply has not done enough intellectual work to be formally acknowledged. They see the work of a medical writer as similar to that of a secretary or, at best, an editor" (Elliott, 2010).

5. "Generally, the work of the medical writer and the agency goes unmentioned, unless they are thanked in the acknowledgements section for writing assistance. [Medical writers] rarely even [see] the published articles [they have] written. In fact...the articles can be pretty hard to track down" (Elliott, 2010).

6. "It is becoming more common for organisations to employ professional editors to assist with medical writing (both papers and grant applications). These editors are often termed 'ghost writers' as their names do not appear on the paper. Some commentators argue that in such cases perhaps no one really qualifies for authorship. The scientists cannot claim authorship since they did not write the work and ghost writers cannot claim it either as they can defend the writing but not the science (Simkhada, van Teijlingen & Hundley, 2013)" (Hundley, van Teijlingen, and Simkhada, 2013).

7. Pharmaceutical companies have "…hired contractors to ghostwrite "false and misleading" articles" with the purpose of claiming the demonstrated safety and efficacy of a medication, "…despite the fact that the study cited failed to demonstrate efficacy in its primary and secondary endpoints [while minimizing] adverse events" (Fugh-Berman, 2013).

8. It is unclear how much raw data ghostwriters are able to view before writing the manuscript. "In fact, one of the extra benefits of this way of working – from a company's perspective – is that the writer will often only see tables and results that have already been prepared by the company statistician, tailored to tell a specific story" (Goldacre, 2012).

9. "[Writer]: I'm given an outline about what to talk about, what studies to cite. They want us to be talking about the stuff that makes the drug look good. [Interviewer]: They don't give you the negative studies? [Writer]: There's no discussion of certain adverse events. That's just not brought up…As long as I do my job well, it's not up to me to decide how the drug is positioned. I'm just following the information I'm given. [Interviewer]: Even though you know that the information is often biased? [Writer]: The way I look at it, if doctors have their name on it, that's their responsibility, not mine (Johnson, 2003)" (Mirowski and Van Horne, 2005).

10. A medical writer described her responsibilities as: "[she] wrote slide kits, monographs, executive summaries, journal articles, backgrounders, newsletters, competitive analyses, publication plans, video scripts, audio scripts, and continuing medical education (CME) programs for physicians and nurses. Each piece ('job', in advertisingspeak) was born out of the publications planning strategy developed for a fee by the medical education (meded) company for the pharmaceutical corporation" (Logdberg, 2011).

11. The problem with ghostwriting "…is the specific ways in which these collaborations [of academics

with medical writers] are disguised, manipulated, and used as tools for marketing drugs" (Moffatt & Elliott, 2007).

12. "Medical writing involves more than just putting the words on the paper[;] Often involves negotiation/liaison[;] May raise ethical issues[;] Often exists at the borderline between science and commerce" (Wager, 2011).

13. "Some countries and organizations have recognized and begun to tackle the problem of ghostwriting and guest authorship. Danish law, for instance, regards misappropriation of authorship as research misconduct (Danish Ministry of Science, Technology, and Innovation, 2005). In regard to ghostwriting, the law on scientific dishonesty, which came into force in 2009, includes the definition of dishonesty as 'false credit given to the author or authors, misrepresentation of title or workplace'" (Bosch, 2011).

14. "Medical writers often have to: liaise between authors and sponsors; liaise with journals…Journals and editors are not all the same…medical writers need to know how to identify and handle different varieties" (Wager, 2011).

*Cross-reference with Acknowledgements, "editorial assistance", "writing support", or "writing assistance" (#24), Guest authors or honorary authors (#28), Non-author contributor(ship) (#34)

(34) NON-AUTHOR CONTRIBUTOR(SHIP)

RELEVANCE:

Non-author contributors are individuals who have made important contributions to a manuscript, but do not meet the criteria for being named as an author under the International Committee of Medical Journal Editors (ICMJE) criteria.

SUPPORT:

1. Contributors who do not meet the four ICMJE criteria for authorship "…should not be listed as authors, but they should be acknowledged. Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding, general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading. Those whose contributions do not justify authorship may be acknowledged individually or together as a group under a single heading (e.g. 'Clinical Investigators' or 'Participating Investigators') and their contributions should be specified (e.g., 'served as scientific advisors,' 'critically reviewed the study proposal,' 'collected data,' 'provided and cared for study patients,' 'participated in writing or technical editing of the manuscript'" (ICMJE, 2015).

2. The definition of non-author contributorship by the ICMJE provides loopholes for medical writers and medical editors to function as ghostwriters without being named as authors. The statement that those who provided "writing assistance" and "participated in writing…of the manuscript" effectively allows for manuscripts to be written by individuals who are not listed as authors in the author byline (Matheson, 2011).

*Cross-reference with Medical writers, medical ghostwriters, or ghost authors (#33)

(35) PUBLICATION PLANNING

RELEVANCE:

Publication planning is a term of academic analysis of the process by which companies strategically shape the scholarly literature base using carefully planned manuscripts with the intention that, once published, the articles contribute to the promotional plan to sell the company's product.

SUPPORT:

1. "Publication planning is the process by which pharmaceutical, biotech, and medical device companies produce and release articles in medical journals and posters at meetings to establish key marketing messages. Some companies employ medical writers and publication planners, and most hire medical education and communication companies (MECCs) to create publications" (Fugh-Berman, 2010).

2. "The business of publication planning established itself during the 1990s, as industry profits were escalating and clinical research was moving out of academic health centres and into contract research organizations. Publication planning is seen as essential to the marketing plan for any new drugs and it begins years in advance of a launch. Publication planners will help a pharmaceutical company design scientific articles that reinforce a larger marketing plan – or, as one agency puts it, help them 'connect data to key messages to support product positioning'... Publication planners will ask how a new drug differs from other drugs on the market, which practitioners need to be reached, and what sort of scientific journals should be targeted. They will debate the finer points of general journals versus throwaways, and the merits of industry-supported journal supplements ("'The value of journal supplements is that [they allow] you to better tailor your marketing message since it is a manufacturer-sponsored publication form'") (Fugh-Berman, 2010).

3. "The details of publication planning can sound arcane to outsiders, yet the business has become large enough to support two international professional societies: an industry-run organization called the International Publication Planning Association, and a non-profit group, the International Society for Medical Publication Professionals. The scientific publications themselves are produced by professional medical writers, many of whom have backgrounds in science" (Elliott, 2010). "Medical journals have high rejection rates, as high as 94% in the case of the Journal of the American Medical Associa-tion and the British Medical Journal. Meanwhile, planning agencies appear to be very successful, claiming, for example, an "acceptance rate on first submission of 94% for abstracts [to conferences] and 78% for

manuscripts [to journals]. Systematic reject-ion is presumably for independent academics, not, it seems, for Big Pharma" (Sismondo, 2011). "Ultimate-ly, pharmaceutical compan-ies demand that publication planners generate revenue by producing and publicizing information that increases sales" (Sismondo, 2011).

4. "In a primer on publication planning, the director of one MECC defines the activity as: 'gaining product adoption and usage through the systematic planned dissemination of key messages and data to appropriate target audiences at the optimum time using the most effective communic-ation channels. These channels are such things as: 'publications, journal reviews, symposia, work-shops, advisory boards, abstracts, educational materials/PR'" (Sismondo, 2007).

5. "Several of the publication planning firms…are owned by major publishing houses. For example, Excerpta Medica is 'an Elsevier business' and writes that its 'relationship with Elsevier allows…access to editors and editorial boards who provide professional advice and deep opinion leader networks'. Wolters Kluwer Health draws attention to its publisher Lippincott Williams & Wilkins, with 'nearly 275 periodicals and 1,500 books in more than 100 disciplines,' and to Ovid and its other medical information provid-ers, emphasizing the links it can make between its different arms" (Sismondo, 2007).

6. "A good publication planner will help identify ways that more than one paper could be produced from each piece of research, so creating a broader palette of promo-tional activities" (Goldacre, 2012).

7. "Typically, a publication plan includes a timeline and lists of articles, grouped under specific messages, with proposed titles and journals to target for submission" (Fugh-Berman and Dodgson, 2008).

8. "Ultimately, pharmaceu-tical companies demand that publication planners generate revenue by producing and publicizing information that increases sales" (Sismondo, 2011).

9. "Pharmaceutical comp-anies have the resources to create rigorous science that supports their marketing plans. In so doing they integrate science and marketing, which we might see as an ethically dubious activity, with problematic consequences for the political economy of knowledge. Were the companies to present their research and marketing material without disguises, [Sismondo] argue[s] that material would often be judged in terms of corporate interests. Thus, the KOLs [key opinion leaders] who disguise those interests are valuable to the extent that they can maintain an appearance of independence" (Sismondo, 2011).

10. "The work of publication planners is largely unseen. To gain commercial value from research, articles publicizing it are written under the names of independent medical researchers, though company authors may also be recognized. The work of pharmaceutical company statisticians, reviewers from a diverse array of departments, medical writers, and the publication planners them-selves is only rarely acknowledged in journal publications (Gotzsche et al., 2007). Even sponsorship, the company funding of the trial, is omitted from many meeting abstracts (Finucane & Bolt, 2004). For this reason, we might see publication planning as the 'ghost management' of medical research and publication" (Sismondo and Doucet, 2010).

*Cross-reference with Ghost management (#26), Involvement of a medical writing organization (MWO) or medical communications company (#30), Involvement of a contract research organization (CRO) or site-management organization (#31)

(36) REPRINTS AND EPRINTS

RELEVANCE:

Reprints are copies of a published article that can be ordered from the journal for wide distribution of a particular study or set of studies. Reprints of a single clinical trial with favourable results for a company can be worth thousands of pages in advertising when distributed to doctors (Leo, Lacasse, & Cimino, 2011; Smith, 2005). Similarly, ePrints are electronic copies of published articles that are available for purchase in multiple units and comply with copyright. ePrints can be downloaded from the publisher for internal and external use (British Library, n.d.).

SUPPORT:

1. "[R]eaders see randomized controlled trials as one of the highest forms of evidence. A large trial published in a major journal has the journal's stamp of approval (unlike advertising), will be distributed around the world, and may well receive global media coverage, particularly if promoted simultaneously by press releases from both the journal and the expensive public-relations firm hired by the pharmaceutical company that sponsored the trial. For a drug company, a favourable trial is worth thousands of pages of advertising, which is why a company will sometimes spend upwards of a million dollars on reprints of the trial for worldwide distribution. The doctors receiving the reprints may not read them, but they will be impressed by the name of the journal from which they come. The quality of the journal will bless the quality of the drug...The evidence is strong that companies are getting the results they want, and this is especially worrisome because between two-thirds and three-quarters of the trials published in the major journals – *Annals of Internal Medicine, JAMA* [Journal of the American Medical Association], *Lancet, and New England Journal of Medicine* – are funded by the industry...Publishers know that pharmaceutical companies will often purchase thousands of dollars' worth of reprints, and the profit margin on reprints is likely to be 70%. Editors, too, know that publishing such studies is highly profitable, and editors are increasingly responsible for producing a profit for the owners. Many owners – including academic societies – depend on profits from their journals. An editor may thus face a frighteningly stark conflict of interest: publish a trial that will bring US$100,000 of profit or meet the end-of-year budget by firing an editor" (Smith, 2005).

*Cross-reference with Promotion in medical journal articles (#18)

(37) TRANSPARENCY OF AUTHORSHIP ROLES

RELEVANCE:

Transparency regarding the roles of various researchers, departments, and companies is important to establish the origination of the manuscript.

SUPPORT:

1. "Authors who 'sign-off' on or 'edit' original manuscripts of reviews written explicitly by pharmaceutical industry employees or by medical publishing companies should offer full authorship disclosure, such as, 'drafting the manuscript was done by representatives from XYZ Inc; the authors were responsible for critical revisions of the manuscript for important intellectual content'" (Ross et al., 2008).

CATEGORY C: DATA SHARING AND DATA TRANSPARENCY

(38) ACCELERATED APPROVAL

RELEVANCE:

Drug companies that are submitting a drug for market approval can request that it is reviewed as part of an accelerated approval program that allows drugs that fill an unmet need and for serious conditions to be granted priority review. The duration of a priority review is shorter than regular review times.

SUPPORT:

1. Accelerated approval is part of a trend toward deregulation for the benefit of industry and, except in a selection of circumstances, does not serve to benefit patients (Goldacre, 2012; Davis and Abraham, 2011).

2. There are some cases in which the length of time that it takes for a drug to be approved may put patients' health at risk; however, there are other cases in which the priority of drug companies is to get their drug approved for market as quickly and cheaply as possible to avoid loss of revenue. Loss of revenue is of concern from the beginning of the drug's research and development process, especially when the drug or parts of it are patented. Patent expiration is a strong commercial incentive, which companies use to pressure governments, which pressure regulators to approve drugs more quickly. The speed of the approval process is typically a key outcome measurement for regulators' performance. Although this pressure comes from both drug companies and regulators, speeding up the approval process for drugs can lead to patient harms. With hastened review processes, data may be of lower quality and the regulator might not impose requirements for strong evidence upon submission and may accept the promise for better studies to follow. This was the case with a drug submission to the United States (US) FDA for midodrine, which "was approved on the basis of three very small, very brief trials (two of them only two days long) in which many of the people receiving the drug dropped out of the study completely. These trials showed a small benefit on a surrogate outcome – changes in blood-pressure recordings when the participants stood up – but no real benefit on real-world outcomes like dizziness, quality of life, falls, and so on. Because of this, after midodrine was approved through the urgent approval scheme, the manufacturer, Shire had to promise it would do more research once the drug was on the market. Year after year, no satisfactory trials appeared [and] fourteen years later, the FDA announced that unless Shire finally produced some compelling data showing that midodrine improved actual symptoms and day-to-day function, rather than some numbers on a blood pressure machine after one day, it would take the drug off the market for good" (Goldacre, 2012).

3. Once a drug is approved for market, it is very rare for a regulator to remove it from the market, especially if the only issue with the submission is lack of efficacy, rather than patient deaths from adverse events. Furthermore, no drug in the US has ever been withdrawn from the market because of a drug company's failure to submit outstanding trial data to the regulator. "Post-marketing trials requested by regulators are often neglected…Accelerated approval is not used to get urgent drugs to market for emergency use and rapid assessment. Follow-up studies are not done. These accelerated approval programmes are a smoke-screen" (Goldacre, 2012).

(39) CLINICAL TRIAL REGISTRATION

RELEVANCE:

The registration of clinical trials in online publicly run and accessible databases helps to ensure that all clinical trials are accounted for and works as a measure to prevent the selective publication of clinical trials. For example, when clinical trials on drugs are registered in ClinicalTrials.gov, the United States National Institutes of Health (NIH) database, trial participants, researchers, and the public are eventually able to determine whether certain trials have been excluded from publication while other favourable trials have been published.

SUPPORT:

1. "The selective publication of clinical trials (clinical bias) and their outcomes (outcome reporting bias) have been identified as major problems distorting scientific evidence", resulting in a skewed literature base that overestimates benefits and downplays harms. "To solve the problem, study registration (disclosure at inception that a study is being conducted) and results registration (posting results after a study has been completed) have been partly implemented using publicly accessible databases. Usually, the details provided at inception and after completion both include information on study methods" (Weisler et al., 2011).

2. An open database in which researchers are compelled to publish their protocol, in full, before beginning clinical trials. This provides the

opportunity for officials or researchers to consult the database to see whether the trials that have been conducted have also been published. Registering clinical trials and their protocols is important because the protocol provides a detailed technical description of all aspects of the trial including the number of patients that will be recruited, where the patients will come from, how the patients will be divided in the trial, what treatment each group of patients will receive in the trial, and what outcome will be measured to establish if the tested treatment was successful. Once this protocol is submitted to the clinical trial registry, it can be used to check not only whether the trial was published, but also if its methods were at all distorted during the trial so that its results were exaggerated. Although journal editors have no legal force, they possess the authority to accept or reject major journal publications. Furthermore, only half of all clinical trials are published and those with unfavorable or negative results are two-times more likely to be suppressed than trials with favorable or positive findings. Without all of these trials both registered and published, there is no way for prescribers and patients to know the true risks of medicines. By insisting on pre-registration of trials, journal editors are helping to take a step forward in data transparency efforts (Goldacre, 2012).

3. All clinical trials are conducted on individual patient participants. The results obtained from each of these individual patients is collected, stored, and summarized in the summary analysis at the end of the study. While patient-level data should not be posted on a publicly available website in a manner in which the patients could be easily identified by their patient histories, patient-level data should be made available to academics who are able to scrutinize the results of the trials. Making this patient-level data, rather than just the summaries, available to academics has notable advantages for prescribers and patients. Making this data available acts as a safeguard against "dubious analytical practices", for example, imposing questionable cut-off-dates for measuring more serious adverse events compared with less serious adverse events that had later measurement dates (VIGOR trial, Vioxx), or switching the primary outcomes described in the protocol (key epoetin trial) (Goldacre, 2012).

(40) DATA SHARING

RELEVANCE:

Data sharing refers to the practice of making the anonymized data from clinical trials publicly accessible. Data sharing is important so that researchers can, in the public interest, interrogate the data to ensure that any published research conclusions were reasonably interpreted from the primary and analyzed data. Data sharing also provides insights into results from both favourable and unfavourable trials so that research efforts are not duplicated regionally or globally.

SUPPORT:

1. Sharing trial data would also allow researchers "to conduct more exploratory analyses of data, and to better investigate – for example – whether a drug is associated with a particular side effect. It would also allow cautious 'subgroup analyses', to see if a drug is particularly useful, or particularly useless in particular types of patients. The biggest immediate benefit from data sharing is that combining individual patient data into meta-analyses gives more accurate results than working with the crude summary results at the end of the paper" (Goldacre, 2012).

2. "In their statements, authors should indicate whether any, all or portions of the data are available to others; where, through whom, when and on what terms data will be available; and how it may be accessed. Some medical journals, such as BMJ [British Medical Journal] and PLoS Medicine [Public Library of Science Medicine], have encouraged data sharing for several years and last year BMJ made data sharing a condition of publication for trials… Ensuring the credibility of published research is the central focus of academic peer review, yet his process is a notoriously poor detector of error or fraud. Existing editorial policies allow editors to ask authors for the original data as part of the peer-review process. However, an individual paper is often reviewed by only a handful of people before publication. Extending the scrutiny of the underlying data into the post-publication period is a logical step" (Fletcher, 2014).

3. Le Noury and colleagues argue that "…although CSRs [clinical study reports] are useful…analysis of adverse events requires access to individual patient level data in case report forms" (Le Noury et al., 2015b).

4. "Clinical study reports represent a hitherto mostly hidden and untapped source of detailed and exhaustive data on each trial. They should be consulted by independent parties interested in a detailed record of a clinical trial, and should form the basic unit for evidence synthesis as their use is likely to minimise the problem of reporting bias…CSRs are usually written for regulators following guidelines developed by the industry regulatory collaborative effort 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use' (ICH)…CSRs are but one category of information that is transmitted from study sponsors to regulators, but are important as they contain substantially more information and detail on the intervention being tested than published versions of the same trial. The wealth of information may be sought with increasing frequency by researchers appraising single trials, entire trial programmes, or by those synthesizing evidence (Chan, 2012; Grens, 2012)…Examination of CSRs revealed scores of important technical contributions to the design, conduct, and reporting of each trial. These included contributions from data-base programmers, records officers and CSR writers, often invisible in the published journal article. In some cases, we found no mention in CSRs of individuals who figured as authors of subsequent published trial reports while individuals named as CSR authors went unacknowledg-ed in journal publications…If the contribution to the trial of most people goes unrecorded, so does their individual

responsibility for what is produced" (Doshi and Jefferson, 2013).

5. "The proactive EMA [European Medicines Agency] policy will provide an easily accessible window to look at CSRs. When you read the statements 'placebo controlled' or 'matching placebo' or 'double blind' in a journal article you can now go and check if that is really the case. And if, for example, the certificate of analysis is missing from the CSR that you are accessing, you can ask EMA why that is so, introducing an unheard degree of accountability. An ever growing body of scientific evidence shows that journals do not give the whole story (although some go to extraordinary lengths). This point reflects simple arithmetic: the ratio of CSR pages to publication pages for the same trial can be as much as 8000 to 1. To maintain their credibility, journals will have to either provide access to CSRs, or stop publishing trials altogether and offer commentaries on trials only. One further option, that of asking for the complete CSR to be made available for each trial on submission, is also at present unrealistic, as current peer-reviewers are unskilled in making sense and reviewing a CSR, especially if time constrained. My experience also tells me that every trial should be looked at in the context of the whole trial programme, for example to avoid a piecemeal approach to the assessment of potential harms" (Jefferson, 2014).

*Cross-reference with Ownership of data (#42)

(41) OFF-LABEL INDICATIONS

RELEVANCE:

It is illegal to promote drugs for uses other than those which have been approved by the applicable national regulatory authority (Lexchin, 2012a).

SUPPORT:

1. "Companies have paid billions of dollars in fines for off-label promotion, often using company-generated company-paid speakers, and ghostwritten articles to imply clinical benefits in the absence of clinical trials (or the presence of negative trials); fines have also been imposed for suppressing risks or misleading clinicians about risks" (Fugh-Berman, 2013).

2. "Prescribing drugs for purposes outside those approved by [an applicable regulatory agency] – 'off-label' use – is common in clinical practice and may be appropriate if well-grounded in solid clinical trial findings (Radley, Finkelstein and Stafford, 2006)…Litigation documents reveal that pharmaceutical companies have paid physicians to promote off-label uses of their products through a number of different avenues…All of the relationships we identified were alleged by whistleblowers with special knowledge of company practices, although none of the complaints were subject to full trial and evaluation by judge or jury. We found that, of 91 authors who had financial relationships with pharmaceutical companies in the context of off-label drug marketing, 39 authored 404 related articles in the three years following their engagement. However, only two-thirds of those articles contained any type of disclosure statement, one-quarter contained a disclosure statement that mentioned the relevant pharmaceutical company and one in seven made disclosures that adequately described their relationship with the manufacturer" (Kesselheim et al., 2012).

3. "The most prevalent strategy involved expanding use on the basis of diagnosis – that is, seeking off-label uses for disease entities distinct from those approved uses by the FDA…The second most common strategy for off-label promotion was to expand the product's use to different variations of the same condition…In some cases, the off-label disease was closely related to the approved one – for example, when a product was specifically approved for a severe manifestation of a condition but then promoted for milder forms…One prominent subcategory of this type of off-label promotion focused on patient subgroups different from those contemplated in the FDA approval…The final, and least common, variety of off-label expansion was off-label prescribing based on different dosing regimens than that approved by the FDA" (Kesselheim, Mello, and Studdert, 2011).

4. "Nearly half of whistleblowers also alleged that manufacturers sought to promote off-label drug use through journal publications…These practices included falsely reporting outcomes from patients in manufacturer-sponsored studies (US ex rel. Gallagher v. Intermune, Inc.) and publishing 'ghostwritten' articles supporting an unapproved use written by the manufacturer under the name of a respected scientist (US ex rel. Westlock v. Pfizer, Inc., et al., 2008). Finally, a minority of whistleblowers alleged that manufacturers recruited physicians to conduct clinical trials for them with the intent of encouraging off-label use ('seeding trials'), rather than for any useful scientific or information-gathering reasons…Many of the complaints describing internal practices…pointed to specific efforts by drug manufacturers to conceal off-label marketing activities. Some described warnings from legal teams to avoid off-label marketing… [which] were widely undermined through strateg-ies such as verbal orders diverging from what was declared in their company policies (US, et al. ex rel. Lauterbach v. Orphan Medical Inc., Jazz Pharmaceuticals Inc., and Dr. Peter Gleason, 2006). For example, one whistleblower reported that his company purposefully designed 'do not detail' labels on materials related to off-label uses that could easily be removed by a sales representative (US ex rel. Collins, et al. v. Pfizer, Inc., 2007). A third of complaints included reports of direct orders to conceal, such as 'cleaning' internal reports and memoranda of all mentions of off-label marketing" (Kesselheim, Mello, and Studdert, 2011).

5. "Our findings show that off-label marketing practices have a broad reach. Similar behaviours and strategies were linked to manufacturers of varying sizes across drugs in virtually all therapeutic classes; they extended to many aspects of the health care system; they affected a multitude of players (prescribers, pharmacies, disease advocacy groups, CME organizations, consumers); and were pursued

through virtually every facet of physician-industry relationships (paid consultancies, preceptorships, and collaboration in clinical trial and research publications)… Nearly a quarter of the whistleblowers alleged that pharmaceutical sales representatives were given access to patients' confidential medical records at physicians' offices for the purposes of trolling for prospective targets for illegal direct-to-consumer promotion of off-label uses" (Kesselheim, Mello, and Studdert, 2011).

6. "Once a drug is on the market, it can be prescribed 'off-label' – that is, for any condition other than that for which the drug was approved. Although it is legal for physicians and other prescribers to prescribe a drug off-label, it is illegal for pharmaceutical companies to promote drugs off-label…It is unknown how much off-label use is due to promotion…Pharmaceutical companies use paid speakers, consultants, and researchers to promote off-label use" (Fugh-Berman, 2013).

*Cross-reference with Promotion in medical journal articles (#18)

(42) OWNERSHIP OF DATA

RELEVANCE:

Transparency pertaining to which institution, research centre, or company owns clinical trial data is important because the owner of the data can dictate the terms of its release and under what terms it can be published.

SUPPORT:

1. As of 2007, approximately 70% of the funding for all clinical trials was sponsored by industry (Sismondo, 2008b). When clinical trials are funded by industry, it is common for academic medical centres to allow drug companies to own the data (Mello, Clarridge, and Studdert, 2005).

2. "The habitual lying took a new turn in 2012 when investors' lawyers accused [a drug company] of having destroyed documents about the development of celecoxib and valdecoxib in bad faith and compounded their initial misconduct by making false statements about the existence of centralised databases (Feeley & Van Voris, 2012). [The drug company] denied the existence of electronic databases containing millions of files about the drugs and argued that the existence of 'e-Rooms were a figment of plaintiffs' imagination'. However, [drug company] officials later acknowledged the rooms existed and turned over documents stored electronically. The lawyers also complained that [the drug company's] technical staff undertook 'two dismantling projects while this case was pending'. In response, [the drug company's] lawyer filed a new lie saying, 'At no time did [the drug company] ever mislead plaintiffs concerning the existence of databases'" (Gotzsche, 2013).

*Cross-reference with Data sharing (#40), Prepublication review and study alteration (#45), Research and clinical trial contractual confidentiality and nondisclosure agreements (#46), Seeding trials (#47), Selective reporting or selective publication of clinical trials (#48)

(43) ORIGINATION OF THE MANUSCRIPT AND MANUSCRIPT OUTLINE

RELEVANCE:

The facility or facilities in which clinical trial manuscripts are actually created and drafted are extremely important to disclose and analyze. It is widely believed that scientific journal articles are written by the named authors within their academic institutions; however, this is not always the case.

SUPPORT:

1. When medical writers are involved in the publication process, they pitch ideas for articles to the drug company that hires their team by "…draw[ing] up justifications for each article to sell the concept within the pharma company. These justifications may be couched overtly in terms of the article's marketing relevance, or more euphemistically in terms of 'medical need' and 'educational value'. Following discussions with the in-house pharma team, more detailed outlines are next developed for approved articles. Around this time 'authors', who are usually leading clinicians (KOLs…) are approached. Next, the outline (though seldom the 'key messages', which generally remain confidential) is introduced to the 'author' and a manuscript is subsequently ghostwritten" (Matheson, 2008). Evidence of scientific manuscripts originating and being tracked by medical writing organizations can be found in the Drug Industry Documents Archive (University of California San Francisco [UCSF], 2015). MECCs or MCCs are jointly responsible "…for the masking of corporate origination within the medical literature" (Matheson, 2011).

2. "Some multicenter trials have publication committees, which may be dominated by in-house or outside investigators, that write up the results for publication. In other cases, the company or CRO writes the reports for publication, circulating draft manuscripts to the investigators who will be listed as authors" (Bodenheimer, 2000).

3. Medical writing organizations may consider manuscript outlines to be "…a concept of an idea", which is developed by "…review[ing] the literature and you see that there is a number of studies and [the idea] can be put in…a summation, which is essentially a review paper… and so what we would do is…scour the literature to see, is there enough information to then be used in a summation document, which is essentially a review paper" (Unknown, 2006). This outline then serves as the beginning to the ghost-written and, subsequently, guest-authored review manuscript. The outline may be sent to the guest author for comments.

*Cross-reference with Origination of data (#44), Prepublication review and study alteration (#45)

(44) ORIGINATION OF DATA

RELEVANCE:

The facility or facilities in which the data was originally collected, analyzed, and stored are extremely important to disclose and analyze. Pharmaceutical companies are involved in every stage of the clinical trial process from designing the protocols to analyzing and publishing the collected data. These companies also own the resultant data and analyses, which leads to questions about which data are published and which are suppressed.

SUPPORT:

1. "Large drug companies often create their own study designs and contract with CROs to develop a network of sites, implement the trial protocol at those sites, and send report forms to the sponsoring company, which performs the data analysis. Smaller pharmaceutical firms may hire a CRO to manage the entire trial, including study design, data analysis, and preparation of [applications to regulators for marketing approval], and journal articles" (Bodenheimer, 2000). "Some trials have four layers (manufacturer, CRO, SMO [site management organization], and physician-investigator), a situation reminiscent of the multitiered managed-care model (employer, health maintenance organization, independent practice association, and physician)… SMOs provide community-physician investigators with administrative support and help market investigators' services to pharmaceutical companies. They have been criticized for producing data of poor quality, inadequately training investigators, and costing more than a system of independent sites unassociated with an SMO" (Bodenheimer, 2000).

2. "A study's raw data are generally stored centrally at the company or CRO. Investigators may receive only portions of the data. Some principal investigators have the capacity to analyze all the data from a large trial, but companies prefer to retain control over this process. A physician-executive at one company explained, 'We are reluctant to provide the data tape because some investigators want to take the data beyond where the data should go" (Bodenheimer, 2000).

3. Without transparency of the facility or facilities in which data was collected and analyzed and without open access to data, the coding of patient reports on side effects, for example, remain unknown and unanalyzed until such data becomes released (Le Noury et al., 2015a, 2015b). The restriction of release of data is often protected by companies' legal experts, whose responsibility is to protect their employers' interests (Matheson, 2008; Parker, 2012).

*Cross-reference with Origination of the manuscript and manuscript outline (#43), Prepublication review and study alteration (#45), Research and clinical trial contractual confidentiality and nondisclosure agreements (#46), Seeding trials (#47)

(45) PREPUBLICATION REVIEW AND STUDY ALTERATION

RELEVANCE:

When clinical trials are funded by industry, it is common for academic medical centres to allow the drug company sponsors to review manuscripts written by the investigators for an agreed-on period before publication (Mello, Clarridge, and Studdert, 2005). Furthermore, when researchers have financial ties including gifts to drug companies that manufacture medications about which they are writing, the sponsor sometimes requires prepublication review of any articles or reports resulting from use of the funds or gifts and this expectation increases when the gifts are biomaterials (Fugh-Berman, 2013). Requesting prepublication review encourages a pro-sponsor environment of manuscript preparation. Disclosure of whether sponsors requested prepublication review as well as any revisions made by sponsors is important in the assessment of industry involvement in manuscript preparation.

SUPPORT:

1. "In recent years… sponsoring companies have become intimately involved in all aspects of research on their products. They often design the studies; perform the analysis; write the papers; and decide whether, when, and in what form to publish the results. In some multicenter trials, authors may not even have access to all their own data" (Angell, 2008).

2. In a 2009 survey, 61% of respondent researchers reported being asked by their research sponsors to give the sponsor prepublication review (Tereskerz et al., 2009).

3. "Even if a researcher does not allow a sponsor to ghostwrite an article, industry review of articles by a sponsor may result in the insertion of subtle marketing messages that researchers may not recognize as advertisements. Marketing messages may not mention the targeted drug; for example, marketing messages may claim that a targeted disease is underdiagnosed, that a mechanism of action is particularly exciting, that a class of drugs has unique benefits, or that a competing drug has significant drawbacks. Marketing messages are disseminated in research studies, case reports, reviews, commentaries, and letters, as well as in presentations and posters at medical meetings (Fugh-Berman & Melnick, 2008)" (Fugh-Berman, 2013).

4. When clinical trials are funded by industry, it is common for academic medical centres to allow drug company sponsors to alter the study design after the clinical trial agreement has been executed (Mello, Clarridge, and Studdert, 2005).

*Cross-reference with Ownership of data (#42), Origination of the manuscript and manuscript outline (#43), Origination of data (#44)

(46) RESEARCH AND CLINICAL TRIAL CONTRACTUAL CONFIDENTIALITY AND NONDISCLOSURE AGREEMENTS

RELEVANCE:

Confidentiality and nondisclosure clauses are typically included in contracts for medical researchers to sign prior to beginning their industry-sponsored studies.

SUPPORT:

1. These clauses are used to "maintain a degree of control over clinical research that is far greater than most members of the public...realize." This is achieved through not only selective disclosure, but also imposed restraints on almost all aspects of the clinical trial process (Mirowski and Van Horne, 2005; Olivieri, 2003; Krimsky, 2004). Similarly, restrictive provisions in clinical trial agreements between industry sponsors and academic medical researchers are typically contractually-binding statements that permit industry sponsors to have very involved roles in the development, conducting, data collection, and data analysis of clinical trials. These roles are usually not disclosed in published clinical trial articles. These restrictive provisions include, but are not limited to, permitting the industry sponsor to revise a manuscript written by investigators (not including revisions related to protecting proprietary information), and gagging clauses that allow sponsors to decide which results should be published (Mello, Clarridge, and Studdert, 2005).

2. It is common for the terms of clinical trial agreements with drug company sponsors of clinical trials to be confidential (Mello, Clarridge, and Studdert, 2005).

3. Site agreements between researchers and industry sponsors of multicenter clinical trials may include provisions concerning: Design of the trial (i.e., plan for data collection, data analysis and interpretation, involvement of an independent data and safety monitoring board), access to data (i.e., whether all data is accessible to authors of reports on multicenter trials, whether site investigators analyze and publish site data, and whether site data may be used for other educational or research purposes), publication of results (i.e., whether all trial results will be published, whether an independent writing or publications committee will have a role, whether criteria for authorship of reports on trial results will be addressed, how decisions will be made about which journals should be considered target journals for the manuscripts on these trials, and whether there is a commitment to publish the results of subsequent research related to original trial), and other issues (i.e. whether confidentiality clauses and other restrictive provisions are permitted and present that restrict rights to publication, how conflicts between the agreement and protocol will be handled, whether the affiliated academic institution is required to follow protocol, and whether the sponsor is required to follow the protocol) (Schulman et al., 2002).

4. "Only 4% [of respondents] reported that a sponsor had ever asked them to withhold research results from publication, but 13% said they had been asked to delay publication of research results. Nearly 8% have been asked by a sponsor to present research results in a way that favours the sponsor's drug or product. About 7% have been asked by an industry sponsor to keep the research results secret. Far more common… were reports of being asked to give the sponsor prepublication review (61%) and being asked to acknowledge the sponsor in the publication (62%)" (Tereskerz et al., 2009).

*Cross-reference with Ownership of data (#42), Origination of data (#44)

(47) SEEDING TRIALS

RELEVANCE:

Seeding trials are clinical trials that are conducted by pharmaceutical companies and are designed to appear to answer a scientific question, but are carried out in order to primarily fulfill the marketing objectives of the sponsoring company. These trials have been used to promote drugs by finding favourable results and increase prescribing in the investigators who become involved in helping to conduct these trials (Krumholz, Egilman, and Ross, 2011; Hill et al., 2008).

SUPPORT:

1. "… [P]hase IV 'seeding' trials [are] trials designed to promote the prescription of new drugs rather than to generate scientific data. In 2004, 13.2% (US$4.9 billion) of R&D expenditures by American pharmaceutical firms was spent on phase IV trials (Pharmaceutical Research and Manufacturers of America, 2006). Almost 75% of these trials are managed solely by the commercial, as opposed to the clinical, division of biopharmaceutical companies, strongly suggesting that the vast majority of these trials are done just for their promotional value (La Puma & Seltzer, 2002)" (Gagnon and Lexchin, 2008).

2. "Pharmaceutical companies use a variety of techniques to promote their products, including 'seeding trials.' Seeding trials are clinical trials, deceptively portrayed as patient studies, which are used to promote drugs recently approved or under review by [an applicable regulatory agency] by encouraging prescribers to use these medications under the guise of participating as an investigator on a clinical trial (Kessler, Rose, Temple, Schapiro and Griffin, 1994). In fact, marketing departments, rather than clinical research departments, are known to design and conduct these trials (Hill, Ross, Egilman and Krumholz, 2008). Although seeding trials are not illegal, they are unethical. Their primary goal is to expose physicians to a new drug and have them interact with the pharmaceutical company sponsor and its sales representatives in order to influence prescribing decisions, independent of any findings from the actual study. In addition, physician 'investigators' are the actual trial subjects, and this information is neither disclosed to them nor the human participants. There are no current estimates of how frequently seeding trials are conducted, and most evidence of their planning

and conduct has come from documents produced in tort litigation against pharmaceutical companies (Kesselheim & Avorn, 2007)" (Krumholz, Egilman, and Ross, 2011).

3. Marketing departments are involved because a considerable number of Phase IV trials are designed to familiarize physicians with products, to encourage prescriptions, or to allow drug representatives more access to prescribers. For example 'seeding trials' pay physicians to prescribe specific drugs as part of trials but are aimed at increasing prescriptions. Thus, pharmaceutical companies also support research by nonacademic physicians…According to one internal document, a goal of the trial was to allow physicians to '[g]ain experience with [a drug] prior to and during the critical launch phase.' For this reason, the trial aimed to enroll 600 primary care physicians rather than a specific number of patients. The prescriptions of those physicians were tracked and compared to a control group of 99 physicians not in the trial. To the extent that data mattered, it was sales data; however, the company presented the trial to physicians as scientific research" (Sismondo, 2011).

4. "Seeding trials are clinical trials designed by pharmaceutical companies to promote the use of pharmacotherapies that were recently approved or are under review by [an applicable regulatory agency]. Seeding trials are designed to appear as if they answer a specific question, but primarily fulfill marketing objectives…[A drug company]'s marketing division…handled the scientific and marketing data, including collection, analysis, and dissemination (Weiner, 2008)" (Hill et al., 2008).

5. Seeding trials are "[c]linical trials of a drug or device among human participants that are conducted for the purpose of promotion of the drug or device and encouraging its use directly to physicians under the guise of their participating as an investigator in a clinical trial, without disclosing the marketing objectives to patients, physicians, regulat-ors, or institutional review board members… These trials may be less likely to be published because they are designed and conducted by marketing. Finally, these trials are often redundant and examine scientific questions that the company has already formally investigated" (Ross, Gross, & Krumholz, 2012).

*See Ezetimibe Plus Simvastatin Versus Simva-statin Alone on Atherosc-lerosis in the Carotid Artery (ENHANCE) trial (Greenland and Lloyd-Jones, 2008), Study of Neurontin: Titrate to Effect, Profile of Safety (STEPS) trial (Krumholz, Egilman, and Ross, 2011), ADVANTAGE trial (Gotzsche, 2013; Hill et al., 2008), Predictable Results and Experience in Diabetes through Intensific-ation and Control to Target: An International Variability Eval-uation (PREDICTIVE) study (Yudkin, 2012).

*Cross-reference with Ownership of data (#42), Origination of data (#44)

(48) SELECTIVE REPORTING OR SELECTIVE PUBLICATION OF CLINICAL TRIALS

RELEVANCE:

Selective reporting or selective publication of clinical trials occurs when favourable results are published, while unfavourable results are suppressed by not publishing them.

SUPPORT:

1. Drug companies conduct many clinical trials. When the results from any of these trials are unfavorable to the company, it can choose not to publish them. These missing, unfavorable trials are important to publish for many reasons including that their not being published distorts the literature base and prevents researchers from truly excluding bias from studies. Selective reporting also keeps negative findings from researchers and funding agencies globally, so that time and money is wasted because they may be conducting those same studies over again, reaching the same unfavorable results, and again failing to publish. In the current publishing environ-ment, failures are simply brushed under the rug, leading to important consequences for the cost of replicating research. It is also important to publish clinical trials that have resulted in negative outcomes or revealed adverse events, which may be unfavorable to the company's profits from that drug, but will undoubtedly be beneficial to prescribers and patients taking those medications. This leads to 'publication bias' where negative results remain unpublished and, therefore, are not subjected to scrutiny or further analysis in meta-analyses or systematic reviews, which are typically used to make drug recommendations in clinical practice guidelines. Further-more, researchers are incentivized by crude publication metrics, such as the number of papers they have published, the number of times that their papers have been cited, and the impact factors of the journals in which they publish. Moreover, positive findings are more likely to be published than negative findings (Goldacre, 2012).

2. "Selective publication of studies that favor a sponsor's drug has obvious commercial benefits. According to the former pharmaceutical execu-tive who shared his persp-ective on the condition of anonymity: 'It is to industry's advantage to selectively support particular researchers whose point of view supports marketing goals, and to encourage selective publication of articles'" (Fugh-Berman, 2013).

3. "In 2002, a Pfizer sponsored meta-analysis was published in the BMJ (Hyde, 2012), which shows how risky it is to collaborate with industry, even for a skilled statistician who has done a lot of good work for the Cochrane Collaboration. The paper surprised many of his Cochrane colleagues when it came out. It claimed that celecoxib leads to fewer serious gastrointestinal events, and the abstract only mentioned relative benefit, not absolute benefit, which was far more modest. The authors only included the misleading 6 months data for the CLASS trial, which was by far the biggest one. What was most strange, however,

was that, although the gastrointestinal events were described in detail over several pages, including many graphs, there were no data on thromboses, which makes the review completely worthless. The authors, one of which was from Pfizer, explained that the review was limited to assessing only upper gastrointestinal safety, with the excuse that the trials did not report on thromboses. This excuse is pathetic. It is irresponsible not to report the number of thromboses, given that is the most important harm of COX-2 inhibitors. Furthermore, the clinicians are obliged to report all serious adverse events immediately to the company, which means that the company must have had data on thromboses, whether or not they preferred to forget about them. In fact, thromboses were reported in the CLASS trial, and even using only the misleading 6 months data, there were 4.3% serious adverse events with celecoxib and 4.2% with the other two drugs, i.e. no advantage at all for celecoxib. The manipulations paid off, as they always do. About 30,000 reprints were bought from the publisher and less than 2 years after its publication, the CLASS trial had already been cited 169 times, and sales increased from $2.6 billion to $3.1 billion in just 1 year. The fraud in JAMA, which has been propagated in many meta-analyses, must have been worth billions of dollars for the company" (Gotzsche, 2013).

*Cross-reference with Ownership of data (#42)

CATEGORY D: ENFORCEMENT

(49) SANCTION: BAN FROM PUBLISHING IN JOURNAL OR ACTING AS A PEER-REVIEWER FOR THAT JOURNAL

RELEVANCE:

A ban from publishing in, or acting as a peer-reviewer for, a journal when a named author has violated the journal's policies has been suggested as a consequence.

SUPPORT:

1. Journal editors should adopt strong sanctions for failure to disclose conflicts of interest, such as a three-year ban on publications within the pages of that journal when an undisclosed conflict of interest is brought to light. The threat of sanctions will improve compliance in this self-regulated field" (Goozner, 2004).

2. "Penalties for misrepresentation of authorship should be severe, because misrepresentation of authorship constitutes fraud, and Plastic and Reconstructive Surgery will investigate cases of ghostwriting and will consider such cases as scientific misconduct. The Journal's policy of investigating instances of plagiarism, duplicate publication, and other forms of scientific misconduct has been previously formulated, and will be applied to allegations of ghostwriting…Plastic and Reconstructive Surgery takes the role of authorship seriously. In publishing a policy statement on authorship criteria, we believe the role of authorship will be clarified and hope that authors will better understand what activities constitute legitimate authorship on their manuscripts" (Sullivan and Rohrich, 2011).

(50) SANCTION: RETRACTION

RELEVANCE:

Retraction refers to the withdrawal of a published study from a journal.

SUPPORT:

1. "Retraction is one of the most serious sanctions a journal can take against authors in cases of misconduct, and can cause permanent damage to reputations and academic careers. Therefore, retractions should be handled carefully and journals should have a process for deciding when and how to retract articles" (Wager & Williams, 2011).

2. "Journal editors and publishers should take responsibility for everything published in their journal. Therefore, if anything misleading, incorrect, or fraudulent is published, it is important that the record is corrected so that readers are not misled. For small errors, such as a misplaced figure legend or an omitted reference, a correction is usually sufficient…However, when large sections or even entire articles are affected, either by misconduct or by honest errors, then a retraction is usually required. The COPE [Committee on Publication Ethics] retraction guidelines state that the purpose of retractions is to correct the literature rather than to punish the authors. Nevertheless, most authors take a negative view of retractions and may fear that they will harm their reputation. It is therefore important that journals have policies to ensure that retraction is used fairly and consistently and also to ensure that the reason for any retraction is always clearly stated. Researchers should be encouraged to notify the journal if they discover a problem with their work and, if this was due to an honest error, should not fear that readers might infer that the resulting retraction was a sign of misconduct. Similarly, authors should not be stigmatized for administrative errors caused by the journal (e.g., if the same article is accidentally published twice). Journals therefore have a duty to ensure that retractions due to misconduct and those due to honest errors are clearly distinguished…In cases of suspected misconduct, editors may want to alert readers to possible problems with an article but may not feel it is appropriate to retract the publication until the investigation has concluded… Retractions are a sign that a journal takes its responsibilities to publication integrity seriously and should never be considered a sign of failure. Peer review cannot be expected to detect all cases of fraud (especially if it is well concealed) or honest errors (which are not even initially visible to authors). Therefore retractions do not necessarily imply failures in the peer review process, although it is always good to learn from experience and consider how such problems might be detected in the future" (Wager, 2015).

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5.12 APPENDIX B MEDICAL JOURNAL POLICY ASSESSMENT TOOL

CATEGORY A: FINANCIAL CONFLICT OF INTEREST DISCLOSURES FOR AUTHORS, RESEARCH TEAM, AND OTHER CONTRIBUTORS

FOCUS: DOES THE MEDICAL JOURNAL POLICY REQUIRE DISCLOSURE OF THESE ITEMS FOR NAMED AUTHORS, INVESTIGATORS, ALL STUDY TEAM MEMBERS, AND CONSULTANTS?

*A CHECKED BOX INDICATES AN ANSWER OF "YES"

ID	ITEM	NO/ UNCLEAR	YES, YEAR RANGES FOR REQUIRED DISCLOSURES				INSTITUTION /COMPANY NAME(S) DISCLOSED?	IS THIS INFORMATION PUBLICLY ACCESSIBLE?	N/A
			PRESENT ONLY	PAST:1-5	PAST: 6-10	PAST: 10+			
A1	Compensation: travel, transportation, attendance, or meeting registration fees at off-site lectures and meetings (i.e., continuing medical education (CME) or research-related activities, travel to advisory boards, consultation, assistance with going to congress)	❑	❑	❑	❑	❑	❑	❑	❑
A2	Conference moderating	❑	❑	❑	❑	❑	❑	❑	❑
A3	Consulting relationships	❑	❑	❑	❑	❑	❑	❑	❑
A4	Extended disclosures (i.e., spouses or partners, adult children, other relatives)	❑	❑	❑	❑	❑	❑	❑	❑
A5	Gifts and meals	❑	❑	❑	❑	❑	❑	❑	❑
A6	Honoraria and payments	❑	❑	❑	❑	❑	❑	❑	❑
A7	Industry support funds for trainees and junior researchers (i.e., scholarships, awards, fellowships)	❑	❑	❑	❑	❑	❑	❑	❑
A8	Industry-funded CME programs	❑	❑	❑	❑	❑	❑	❑	❑
A9	Industry-funded speaking relationships/speakers' bureaus	❑	❑	❑	❑	❑	❑	❑	❑
A10	Institutional or company affiliations and employment	❑	❑	❑	❑	❑	❑	❑	❑
A11	Paid expert testimony in court case	❑	❑	❑	❑	❑	❑	❑	❑
A12	Patents/royalties	❑	❑	❑	❑	❑	❑	❑	❑
A13	Payment for working on or enrolling patients in clinical trials	❑	❑	❑	❑	❑	❑	❑	❑
A14	Promotional visits with drug sales representatives	❑	❑	❑	❑	❑	❑	❑	❑
A15	Receipt of drug samples	❑	❑	❑	❑	❑	❑	❑	❑
A16	Restricted and unrestricted grants	❑	❑	❑	❑	❑	❑	❑	❑
A17	Scientific advisory board memberships, consultants meetings, board of directors appointments, review panel participation	❑	❑	❑	❑	❑	❑	❑	❑
A18	Stock ownership or options, bonds, and equity holdings	❑	❑	❑	❑	❑	❑	❑	❑

A19	Work with a practice management consultant	❑	❑	❑	❑	❑	❑	❑	❑
A20	Financial interests related to the funder(s) of study	❑	❑	❑	❑	❑	❑	❑	❑
A21	Financial interests related to the competitor(s) of the funder(s) of the study	❑	❑	❑	❑	❑	❑	❑	❑
A22	Personal financial gain from this study	❑	❑	❑	❑	❑	❑	❑	❑
A23	Financial gain for employing institution/company from this study	❑	❑	❑	❑	❑	❑	❑	❑

CATEGORY B: ROLES IN THE RESEARCH, WRITING, AND PUBLICATION PROCESSES

FOCUS: DOES THE MEDICAL JOURNAL POLICY REQUIRE THE *DISCLOSURE AND DESCRIPTION* OF RESPONSIBILITIES AND PARTICIPATION OF PEOPLE/COMPANIES IN THE FOLLOWING ROLES FOR A SUBMITTED STUDY?
*A CHECKED BOX INDICATES AN ANSWER OF "YES"

ID	ITEM	NO/ UNCLEAR	YES, YEAR RANGES FOR REQUIRED DISCLOSURES				INSTITUTION /COMPANY NAME(S) DISCLOSED?	IS THIS INFORMATION PUBLICLY ACCESSIBLE?	N/A
			PRESENCE IN ROLE ONLY	START DATE	END DATE	PREVIOUS ROLES			
B24	Named author(s)	❑	❑	❑	❑	❑	❑	❑	❑
B25	Principal investigator(s)	❑	❑	❑	❑	❑	❑	❑	❑
B26	Co-investigator(s)	❑	❑	❑	❑	❑	❑	❑	❑
B27	Paid consultant(s)	❑	❑	❑	❑	❑	❑	❑	❑
B28	Members of steering committee	❑	❑	❑	❑	❑	❑	❑	❑
B29	Participant recruiter(s)	❑	❑	❑	❑	❑	❑	❑	❑
B30	Funder(s)	❑	❑	❑	❑	❑	❑	❑	❑
B31	Type of support provided by funder(s) (i.e., provision of financial, equipment, testing kit, drug, or device resources?)	❑	❑	❑	❑	❑	❑	❑	❑
B32	Research assistant(s)	❑	❑	❑	❑	❑	❑	❑	❑
B33	Contract research organization(s)	❑	❑	❑	❑	❑	❑	❑	❑
B34	Medical writing organization(s)	❑	❑	❑	❑	❑	❑	❑	❑
B35	Medical writer(s) or medical editor(s)	❑	❑	❑	❑	❑	❑	❑	❑
B36	Corresponding author/liaison	❑	❑	❑	❑	❑	❑	❑	❑
B37	Statistician(s)	❑	❑	❑	❑	❑	❑	❑	❑
	Observer(s)	❑	❑	❑	❑	❑	❑	❑	❑

ID	ITEM[1]	NO	ULTIMATE AUTHORITY AND/OR RESPONSIBILITY FOR OVER STUDY PROCESS COMPONENTS[1]				INSTITUTION /COMPANY NAME(S) DISCLOSED?	IS THIS INFORMATION PUBLICLY ACCESSIBLE?	N/A
			STUDY TEAM	FUNDER	SHARED	UNCLEAR			
B38	Conceptualizing and designing the study	❑	❑	❑	❑	❑	❑	❑	❑
B39	Approving the final design	❑	❑	❑	❑	❑	❑	❑	❑
B40	Approving the final data analysis plan	❑	❑	❑	❑	❑	❑	❑	❑

[1] Based on Rochon and colleagues. Financial conflict of interest checklist 2010 for clinical research studies (2010).

B41	Recruiting participants	❑	❑	❑	❑	❑	❑	❑	❑
B42	Collecting or assembling data	❑	❑	❑	❑	❑	❑	❑	❑
B43	Analyzing the data	❑	❑	❑	❑	❑	❑	❑	❑
B44	Interpreting the data	❑	❑	❑	❑	❑	❑	❑	❑
B45	Supervising or coordinating the study	❑	❑	❑	❑	❑	❑	❑	❑
B46	Deciding on the dissemination plan related to study results	❑	❑	❑	❑	❑	❑	❑	❑
B47a	Deciding whether a drug's off-label indications will be analyzed and/or recommended in manuscript	❑	❑	❑	❑	❑	❑	❑	❑
B47b	Approved indication of the drug in the journal's country of publication	❑	❑	❑	❑	❑	❑	❑	❑
B48	Drafting all or parts of the manuscript	❑	❑	❑	❑	❑	❑	❑	❑
B49	Revising the manuscript for important intellectual content	❑	❑	❑	❑	❑	❑	❑	❑
B50	Final approval of the version of the manuscript to be published	❑	❑	❑	❑	❑	❑	❑	❑
B51	Deciding target journal for publication	❑	❑	❑	❑	❑	❑	❑	❑
B52	Deciding the timing of the manuscript submission for publication	❑	❑	❑	❑	❑	❑	❑	❑
B53	Deciding authorship	❑	❑	❑	❑	❑	❑	❑	❑
B54	Deciding authorship order	❑	❑	❑	❑	❑	❑	❑	❑
B55	Acting as study guarantor	❑	❑	❑	❑	❑	❑	❑	❑
B56	Corresponding author	❑	❑	❑	❑	❑	❑	❑	❑
B57	Providing administrative, technical, or logistic support	❑	❑	❑	❑	❑	❑	❑	❑
B58	Registering the clinical trial	❑	❑	❑	❑	❑	❑	❑	❑
B59	Ownership of data	❑	❑	❑	❑	❑	❑	❑	❑

CATEGORY C: ENFORCEMENT AND SANCTIONS

FOCUS: DOES THE MEDICAL JOURNAL POLICY HAVE CLEAR ENFORCEMENT MECHANISMS AND SANCTIONS FOR NON-COMPLIANCE?

ID	ITEM	NO	UNCLEAR	YES	IS THIS INFORMATION PUBLICLY ACCESSIBLE?	N/A
C60	Is there a party responsible for policy enforcement?	❑	❑	❑	❑	❑
C61	Is there a clear process by which the medical journal enforces the policy?	❑	❑	❑	❑	❑
C62	Does the journal have a range of sanctions that can be enforced should the policy be violated at various levels of seriousness?	❑	❑	❑	❑	❑
C62a	Rejection of article	❑	❑	❑	❑	❑
C62b	Amendment to material	❑	❑	❑	❑	❑
C62c	Relabeling of material	❑	❑	❑	❑	❑

C62d	Label published on electronic version of article (i.e., “Notice of correction: this paper has been corrected because of violations A, B, and C. See addendum for details).	❑	❑	❑	❑	❑
C62e	Author suspension from publishing	❑	❑	❑	❑	❑
C62f	Retraction of article	❑	❑	❑	❑	❑
C62g	Are the enforced sanctions made public?	❑	❑	❑	❑	❑

INTEGRATIVE DISCUSSION

Peer-reviewed medical journals are, arguably, the most trusted source for the highest forms of clinical evidence that physicians can rely on and apply in their medical practices. However, medical research is increasingly being defined, conducted, interpreted, and published by for-profit entities that comprise the drug promotion industry. The pervasive roles of contract research organizations, medical writing organizations, and drug companies in the medical research and publishing processes have transformed the way in which medical science is conducted, interpreted, and disseminated. Chapter 5 first provided an analysis of neoliberal science through considering the roles of employees at contract research organizations and medical writing organizations. This chapter also analyzed the resultant fragmentation of the research and authorship roles, which are divided amongst for-profit entities that decide when to involve the physicians who will be named as authors on the published studies.

In Chapter 5, a literature review of sources that have critically analyzed the involvement of industry in the medical research and publishing processes resulted in a glossary of 50 key terms. Each of these terms is accompanied by a definition and supporting content from the sources assessed during the literature review. The terms from the glossary were, subsequently, thematically categorized and appropriated to create a assessment tool. This assessment tool has the central purpose of assisting in the assessment of transparency throughout medical research via disclosures of financial conflict of interest relationships and the roles and responsibilities of the authors and other contributors to manuscripts that are submitted to medical journals. In consultation with

the glossary, the transparency of roles and responsibilities that results from use of the assessment tool can help journal editors to predict submissions that are likely to be biased as a result of FCOI relationships and the involvement of drug promotion industry entities throughout the research and publication processes.

Medical journals are an important medium by which medical research and knowledge is disseminated to physicians. In fact, medical journals are so highly regarded that some professional medical associations (PMAs) will accredit journal clubs as continuing medical education (CME) activities. PMAs are similarly highly regarded organizations that unite physician specialties and provide CME opportunities for their members. Because accredited CME programs across specialties have received financial support from industry, the content of the programs has been questioned. Furthermore, even when these programs do not receive commercial funding, sessions may still be conducted by speakers who have financial relationships with industry. The next manuscript (Chapter 6) examines the policies adopted by PMAs pertaining to industry involvement in accredited CME programs.

CHAPTER 6

CONTINUING MEDICAL EDUCATION AND PHARMACEUTICAL INDUSTRY INVOLVEMENT: AN EVALUATION OF POLICIES ADOPTED BY 60 CANADIAN PROFESSIONAL MEDICAL ASSOCIATIONS

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6.1 SUMMARY

Introduction

Professional medical associations (PMAs) play a crucial role in providing accredited continuing medical education (CME) to physicians. Funding from the pharmaceutical industry may lead to biases in CME. This study examines publicly available policies on CME, adopted by Canadian PMAs as of December 2015.

Methods

Policies were evaluated using an original scoring tool comprising 21 items, two questions about PMAs' general and CME funding from industry, and three enforcement measures.

Results

We assessed 235 policies adopted by 60 Canadian PMAs (range, 0 to 32). Medical associations received summative scores that ranged from 0% to 52.4% of the total possible points (maximum score=63). Twenty-six associations received an overall score of 0%. The highest mean scores were achieved in the areas of commercial involvement in planning CME activities (mean: 1.1/3), presence of a review process for topics of CME activities (mean: 1.1/3), content review for balanced information (mean: 1.1/3), and responsibility of distribution of funds (mean: 1.0/3). The lowest mean scores were achieved in the areas of awards (mean: 0.0/3), industry personnel, representatives, and employees (mean: 0.1/3), distribution of industry-funded educational materials at CME activities (mean: 0.1/3), and distinction between marketing and educational materials (mean: 0.1/3).

Discussion

These results suggest that Canadian PMAs' policies on industry involvement in CME are generally weak or non-existent; therefore, the accredited CME that is provided to Canadian physicians may be viewed as open to bias. We encourage all Canadian medical associations to strengthen their policies to avoid the potential for commercial influence in CME.

KEYWORDS: Continuing medical education (CME), Canadian professional medical associations (PMAs), physician education, pharmaceutical industry, scoring tool, policy evaluation

6.2 INTRODUCTION

Professional medical associations (PMAs) provide members with professional educational opportunities including accredited continuing medical education (CME) or continuing professional development (CPD); hereinafter, collectively referred to as CME. However, the CME that these organizations offer may be undermined because of a perception of bias due to funding that they receive from pharmaceutical and medical device companies (Bernat, Goldstein, & Ringel, 1998; Kassirer, 2007; Relman, 2001; Rothman et al., 2009).

It is important for physicians to participate in CME to not only maintain their credentials, but also to keep informed of new pharmaceutical and non-pharmaceutical treatments. The integrity and credibility of CME provided by medical associations has been questioned because it has become so closely linked with the marketing initiatives of the pharmaceutical industry (Avorn & Choudhry, 2010; Relman, 2001, 2003; Spithoff, 2014). Data from the United States (US) suggests that, in 2014, commercial support accounted for approximately 25% of total income reported by CME providers (Accreditation Council for Continuing Medical Education [ACCME], 2015). Although industry representatives maintain that the intention of their funding of CME is motivated by the desire to provide up-to-date information to doctors, researchers independent from industry suggest that this financial support is used to advance sponsors' marketing interests (Relman, 2001; Rodwin, 2010; Steinbrook, 2008). Funding for CME is generally paid out of companies' marketing budgets, which are dedicated to producing sales (Relman, 2001). Fugh-Berman and Hogenmiller (2015) argue that even when CME

activities have not received commercial funding, speakers who are funded by industry can still be used.

Tools developed for evaluating the potential for bias within CME presentations do not evaluate the policies that medical associations have adopted to guide industry involvement prior to the CME event (Barnes et al., 2007; Dyck & Kvern, 2008; Takhar et al., 2007). The purpose of this study is twofold: we present an original tool for evaluating policies adopted by PMAs concerning financial conflict of interest (FCOI) relationships and industry involvement in CME. We, then, use the tool to conduct a systematic evaluation of CME policies that have been adopted by Canadian PMAs.

6.3 METHODS

6.3.1 Creation of the scoring system

The items included in the tool for evaluating the policies of the PMAs were compiled based on the works by Barnes and colleagues (2007), Dyck and Kvern (2008), Takhar and colleagues (2007), Kassirer (2007), and Rothman and colleagues (2009).

Three experts (see Acknowledgements) independently reviewed both the list of items and the draft scoring system for face validity. The tool was modified based on their feedback regarding clarity and consistency between scores so that the range of scores for each item had comparable restrictiveness.

The two authors pilot tested and modified the items and the scoring system based on the policies of 10 Australian PMAs. Australian associations were deemed to be appropriate for the pilot test because the Australian medical system is broadly similar to that of Canada. Further refinements were made to the scoring tool in the process of the actual policy reviews.

The final scoring tool comprises 21 categories, two questions, and three enforcement measures. Each of the 21 categories is rated on a 4-point scale, where 0=no policy found, 1=weak or permissive policy, 2=moderate policy, and 3=strong or restrictive policy (6.11 Appendix 1). Therefore, the highest attainable score is 63, while the lowest possible score is 0. Across items in the scoring tool, a score of 3 indicates no commercial involvement and no financial ties with industry. A score of 2 indicates that, where there is industry involvement in planning or presenting CME programs, the PMA retains ultimate authority. A score of 1 indicates that the item was addressed in the policy, but that industry involvement was still permitted without clearly stating that the PMA retained ultimate authority over CME decisions. Scores for each PMA are expressed as percentage of the maximum possible score.

The two questions (Q1 and Q2) inquire about PMAs' general and CME funding from industry. The three enforcement measures (EA, EB, and EC) seek to determine whether a party is clearly identified as being responsible for general oversight to ensure compliance, sanctions for noncompliance (Shnier, Lexchin, Mintzes, Jutel, & Holloway, 2013), and investigations into noncompliance (6.11 Appendix 1). The results of the questions and enforcement measures are represented as binary outcome measures (i.e.,

yes or no). We did not attempt to ascertain whether PMAs' policies had been violated, nor did we measure the severity of the sanctions identified within policies.

One author initially scored policies for all of the PMAs and the second author independently conducted duplicate scoring for each fifth PMA policy. Results were compared and disagreements were resolved through discussion.

6.3.2 Policy collection

We obtained a list of 58 PMAs from the Royal College of Physicians and Surgeons of Canada (RCPSC) website (http://www.royalcollege.ca/rcsite/resources/national-specialty-societies-e). We also included the College of Family Physicians of Canada (CFPC) and the RCPSC (hereinafter collectively included within the definition of PMAs). The RCPSC was included because many of the individual PMAs referenced its policies and because it also accredits CME. Similarly, the CFPC accredits CME for family physicians. Therefore, we searched the websites of 60 associations for publicly available English-language policies, guidelines, or interpretive documents (hereinafter collectively referred to as "policies") specifically related to accredited CME activities. An example of an interpretive document is a conflict of interest disclosure form. We limited our search to publicly available policies because we felt that they need to be readily accessible in order to ensure public trust in the operation of these associations and so that doctors are able to assess how commercial involvement in CME is dealt with before they attend events.

When PMAs' websites had search-bars, we used the search terms "policy", "policies", "accreditation", "accredited", "medical education", "continuing medical education", "CME", and "continuing professional development", "CPD" to locate the policies. When using the search bar did not return any results or in the absence of a search bar, we made an effort to manually search the association's website to find policies.

When PMAs' websites referred to external documents, but provided no link to them, we did not collect these documents. Additionally, when PMAs referred to general college websites, such as that of the RCPSC, but did not provide the link to a particular policy, we did not conduct a search of the external site. When PMAs provided documents from, or direct links to, industry codes (i.e., Rx&D Code of Conduct (Rx&D, 2012) MEDEC Code of Conduct (MEDEC, 2015)) we did not evaluate these documents because the PMAs cannot enforce or modify industry codes.

We recorded the titles of policies and the adoption or most recent review dates. If more than one policy was included within a document and the policies had different dates, the most recent date within the overall document was considered to apply to all contained policies. A primary collection of policies was conducted from June 30, 2015 to July 4, 2015 with a secondary collection from December 1, 2015 to December 7, 2015. At this latter time, we also recorded whether associations' websites identified having received pharmaceutical industry sponsorship within the last five years for overall societal activities and for its accredited CME.

When more than one policy per society addressed an item in the scoring tool, the highest score was taken for final calculation of the association's score for that item. We report overall scores for each association and the mean score for each of the 21 items.

6.4 RESULTS

We assessed 235 policies, which were collectively adopted by 60 Canadian PMAs (range, 0 to 32 policies per association). Eight documents were inaccessible ("page not found" or "link broken": 7 documents, password login required to view policy: 1 document) (6.12 Appendix 2). The dates of 112 documents were not provided. The remaining 123 policies ranged in date from 2004 to 2015. One document was more than 10 years old, while 68 were adopted within four years of December 2015 (6.12 Appendix 2).

The Canadian Medical Association's policy on physicians' interactions with industry (Canadian Medical Association [CMA], 2007) was formally adopted by 22 out of 60 Canadian medical associations, while 30 associations reference it in their own policies. For the RCPSC guidelines, the corresponding numbers are 15 and 20, respectively.

Twenty-six associations received an overall score of 0/63 (0%), indicating that these associations either had no policies or that their policies did not address the items in the scoring tool. The remaining 34 medical associations received scores that ranged from 1/63 (1.6%) to 33/63 (52.4%) (median: 25.0 (41.7%), interquartile range [IQR]: 21.3 to 26.0 (35.4% to 43.4%)). No items in any policy received a score of 3, which represents the greatest restrictiveness in terms of industry involvement (Table 6.1).

The highest mean scores (1.1/3) were achieved in the areas of commercial involvement in planning CME activities, presence of a review process for topics of CME activities, content review for balanced information, and responsibility of distribution of

funds (mean: 1.0/3). The lowest mean scores (0.1/3) were achieved in the areas of industry personnel, representatives, and employees, distribution of industry-funded educational materials at CME activities, and distinction between marketing and educational materials (Table 6.1). None of the 21 items were addressed by all policies. Awards was not addressed by any association, while the most frequently addressed item was presence of a review process for topics of CME activities (33 of 60 associations) (Table 6.1).

Twenty-three (38%) PMAs publicly disclosed that they accepted industry sponsorship (Q1), while 49 (82%) PMAs received industry sponsorship specifically for CME activities (Q2). The policies adopted by 33 of the 60 medical associations identified a party responsible for oversight to ensure compliance (EA) (Table 6.2), e.g., the "planning committee" or "chair of the planning committee" (Royal College of Physicians and Surgeons of Canada [RCPSC], n.d.-a). Seventeen of the 60 medical associations identified sanctions for noncompliance with the policies, e.g., an RCPSC COI disclosure form stated that "Failure to disclose or false disclosure may require the Planning Committee to replace the speaker" (RCPSC, n.d.-a). The College of Family Physicians of Canada adopted the most extensive description of action in cases of CFPC policy violation (The College of Family Physicians of Canada [CFPC], 2014). None of the medical associations stated within their policies that the results of the investigations into noncompliance would be made accessible on the society's website.

6.5 DISCUSSION

The 60 Canadian professional medical associations received scores that ranged from 0% to 52.4% of the maximum possible score. Half of the medical associations received scores of 16/63 (25.4%) or lower. The remaining 30 medical associations received scores between 17/63 (27.0%) and 33/63 (52.4%). Out of the 123 policies where dates were provided, 68 were developed within the previous 4 years. Therefore, in these cases we do not feel that the poor scores reflect older policies that may have been adopted before FCOI became a concern.

In general, the items that had the highest mean scores received scores of 2/3 indicating that the medical associations retained complete control over the planning and topics of CME activities and were responsible for ensuring the validity and objectivity of educational material. The item concerning responsibility for distribution of funds usually received a score of 2/3 indicating that PMAs' CME committees held the responsibility for distributing grants from industry. The RCPSC has stated that companies that provide educational grants possess "…legal obligations to ensure any financial support provided is directed to a specific event or activity" (Royal College of Physicians and Surgeons of Canada [RCPSC], n.d.-b).

The lowest scores were received in the areas of awards (mean: 0.0/3), industry personnel, representatives, and employees, distribution of industry-funded educational materials at CME activities, and distinction between marketing and educational materials (mean: 0.1/3). Only 12 out of 60 medical associations addressed the item regarding funding for CME activities in their policies, mean score of 0.2/3 (Table 6.1), indicating

that medical associations tend to permit one or more commercial sponsors to provide funding for CME events.

Scores of 1/3 indicate permissiveness and tend to have an effect which is equal to that of a non-existent policy. However, it was important to distinguish between areas where even permissive policies existed and where policies were non-existent. This distinction allows CME participants and providers to identify the areas that have been addressed, even if permissively, as opposed to completely left out.

Given the number of medical associations that formally include or reference the guidelines from either the Canadian Medical Association or the Royal College of Physicians and Surgeons of Canada, if one or both of these associations changed their guidelines, those changes would have a wide ranging effect.

Critics of conflict of interest regulation might argue that adopting and enforcing stringent policies assumes wrongdoing and attaches blame to the individual or institution engaging in the financial relationship (Brody, 2010). However, and importantly, this criticism may not appreciate the degree to which institutional FCOI relationships could threaten not only the trust that physicians and patients have in the roles of associations (Brody, 2010), but also the independence of the content included within CME programs (Katz, Goldfinger, & Fletcher, 2002).

International literature on institutional financial relationships between PMAs and commercial industry supports the need for critical analysis of their policies on industry involvement and influence in CME activities. Cosgrove and Bursztajn (2010) argue that if CME activities are sponsored by industry, the completeness and accuracy of the

educational information provided may be not only incomplete, but also biased. They recommend a system of checks and balances and clear enforceable policies to safeguard against the potential for industry influence in the CME activities in which physicians participate.

Kesselheim and colleagues (2011) found that off-label prescribing of medications by physicians was encouraged through teaching and research activities, including CME. In over half of the cases in their study, speakers chosen for CME were known to promote off-label medication use. Steinman and colleagues (2006) found that drug companies use CME activities as a venue for direct-to-physician promotion to convince both current prescribers and non-prescribers to increase new prescriptions.

It is possible for PMAs to reduce their financial dependence on, and relationships with, industry. At its annual meeting and CME conferences, the North American Spine Society prohibits company logos on promotional items and does not sell lists of CME participants to companies in order to prevent "robo calls" to participants' hotel rooms at CME events. It further rejects funding for meals and snacks at its CME events. To account for the decrease in industry funding for CME, annual membership and meeting registration fees and fees charged for exhibit hall booths were increased modestly. Despite these modest increases, physician membership has also increased (Schofferman et al., 2013). The Oregon Academy of Family Physicians no longer accepts any grants, restricted or unrestricted, for its CME events or allows drug companies to have booths in its exhibit hall during conferences (Silverman, 2008). In response to the increasing awareness and concern over industry's influence via financial relationships, over 100

large medical institutions in the US severed their financial ties with industry (Wilson, 2010).

In Canada, CME programs for physicians receive a substantial portion of funding from pharmaceutical and medical device companies, although it is widely accepted that industry involvement in education influences physicians' prescribing choices (Spithoff, 2014; Tabas et al., 2011). It is unlikely that companies would donate substantial funds without any expectation of return from increased sales (Spithoff, 2014).

6.6 LIMITATIONS

Although we attempted to make the scoring tool as universally applicable as possible, some associations' policies and documents included important areas for which the scoring tool did not account, for example peer selling and FCOI of CME moderators or facilitators. We view our tool as a living document that needs further study and refinement and in this process these additional items and other areas should be addressed.

We attempted to do a thorough search of each association but it is possible that the key words that we used and our manual searches missed relevant policies.

Where policies did not directly reflect the content of the scoring system, we had to determine if their contents complied with the spirit of the scoring system and, therefore, our interpretation of the policy may have had a subjective element. Importantly, the overall score for each policy for a single item may have been based on more than one phrase in one or more policies of a PMA. Although the scoring tool

separated FCOI into many discrete activities, associations' policies were not necessarily structured in the same way. Therefore, a clause in a policy could have been relevant to more than one item in the tool and, as a result, would have been scored under both items.

We did not contact medical associations to see if they were in agreement with our assessments. We also evaluated policies without analyzing any CME events sponsored by these associations. Despite permissive policies, CME events accredited by PMAs might still be free of possible industry bias. A comparison of policies and practice is an area for future research in order to determine the extent to which policies are enforced. Finally, although we attempted to ensure that our tool had face validity by having it peer reviewed we recognize that there will always be an element of subjectivity in any such tool.

6.7 CONCLUSION

We conducted a comprehensive evaluation of the policies on CME activities and industry involvement adopted by 60 Canadian medical associations. We found the policies to be generally weak or non-existent. This weakness was coupled with the majority of associations having disclosed industry sponsorship for CME activities in the last five years.

In order to avoid institutional FCOI relationships with industry, PMAs should avoid seeking and accepting industry funding for CME activities. Alternative mechanisms for financing CME activities may include modestly increasing membership

dues and registration costs (Pellegrino & Relman, 1999). Another approach might include lobbying provinces to reimburse physicians for attending CME events and some provinces have already taken this initiative (Marlow, 2004). PMAs could also lessen possible bias by only accepting anonymous industry sponsorship, a move recommended by a recent report from the College of Family Physicians (Task Force on the CFPC's Relationship with the Health Care/Pharmaceutical Industry (HPI), 2013).

The Canadian PMAs ought to take a leadership position on behalf of their physician members and the patients that they serve when it comes to acceptable conduct in the context of FCOI relationships (Pellegrino & Relman, 1999). We urge the medical associations that have not adopted any policies to, at the very least, adopt the policies from the Royal College of Physicians and Surgeons of Canada and the Canadian Medical Association. We also encourage Canadian PMAs to review and strengthen their policies to protect the integrity of the education that Canadian physicians are receiving and applying in the treatment of their patients.

6.8 LESSONS FOR PRACTICE

- Currently, PMAs in Canada generally allow pharmaceutical industry involvement in, and funding of, CME for physicians.
- The majority of PMAs in Canada disclosed having received funding from drug companies for CME in the last 5 years.
- PMAs' policies on industry involvement in, and funding of CME, coupled with the disclosures of industry sponsorship of CME by Canadian PMAs indicates that these programs may be vulnerable to bias.
- There are methods by which PMAs can fund CME for physicians without financial assistance from industry.

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TABLE 6.1: SCORING TOOL ITEMS AND SUMMARY OF RESULTS BY ITEM

Item	No. of PMAs (%) with no policy (score=0)	No. of PMAs (%) with permissive policy (score=1)	No. of PMAs (%) with moderate policy (score=2)	No. of PMAs (%) with restrictive policy (score=3)	Mean score per item, *x*/3
Commercial involvement in planning CME activities	28	0	32	0	1.1
CME committee members' involvement in CME activity planning decisions	49	6	5	0	0.3
Presence of a review process for topics of CME activities	27	1	32	0	1.1
Control over CME activity speakers	31	3	26	0	0.9
Speakers: Financial conflict of interest disclosures at CME activities	28	19	13	0	0.8
CME committee members and officers: Financial conflict of interest disclosures at CME activities	29	19	12	0	0.7
Review of educational materials by CME committee A. Content review for balanced information	28	1	31	0	1.1

B. Origination of content	33	26	1	0	0.5
Funding for CME activities	48	10	2	0	0.2
Disclosure and transparency for CME activities	30	30	0	0	0.5
Responsibility of distribution of funds	29	3	28	0	1.0
Awards	60	0	0	0	0.0
Industry personnel, representatives, and employees	56	3	1	0	0.1
Distribution of industry-funded educational materials at CME activities	57	3	0	0	0.1
Distinction between marketing and educational events	55	3	2	0	0.1
Branded items	31	23	6	0	0.6
Exhibit halls and booths	35	24	1	0	0.4
Use of brand or trade names	30	28	2	0	0.5
Promotion of unapproved uses or off-label indications	33	0	27	0	0.9
Sharing attendee information	35	25	0	0	0.4
Satellite symposia	33	1	26	0	0.9

TABLE 6.2: SUMMARY OF RESULTS BY PROFESSIONAL MEDICAL ASSOCIATION

Name of association	Total score out of 63 (%)	Does the medical association publicly disclose on its website that it has industry† funding generally, unrestricted, or otherwise? (Yes/No)	Does the medical association publicly disclose on its website industry funding specifically for CME activities? (Yes/No)	Enforcement of CME-related policy/section of policy		
				Is it clear within the policy that there is a party responsible for general oversight to ensure compliance? (Yes/No)	Is it clear within the policy that there are sanctions for noncompliance? (Yes/No)	Is it clear within the policy that the results of investigations into noncompliance will be publicly accessible on the association's website? (Yes/No)
Association of Medical Microbiology and Infectious Disease Canada	0 (0)	No	Yes	No	No	No
Canadian Academy of Child and Adolescent Psychiatry	0 (0)	No	Yes	No	No	No
Canadian Academy of Geriatric Psychiatry	0 (0)	No	Yes	No	No	No
Canadian Academy of Psychiatry and the Law	9 (14)	No	Yes	No	No	No
Canadian Academy of Sport and Exercise Medicine	0 (0)	Yes	Yes	No	No	No
Canadian Anesthesiologists' Society	26 (41)	No	Yes	Yes	Yes	No

† "Industry" refers to any commercial, for-profit company including but not limited to pharmaceutical and medical device companies as well as advertising agencies, including medical education communication companies (MECCs) (Steinbrook, 2008), whose purpose is to develop promotional materials often labelled as "educational" or "continuing medical education" (CME) materials that promote their clients' products and services. MECCs may be accredited to provide CME (Relman, 2001).

Canadian Association of Emergency Physicians	18 (29)	No	Yes	Yes	No	No
Canadian Association of Gastroenterology	22 (35)	Yes	Yes	Yes	No	No
Canadian Association of General Surgeons	25 (40)	No	No	Yes	No	No
Canadian Association of Interventional Cardiology	0 (0)	Yes	No	No	No	No
Canadian Association of Medical Biochemists	0 (0)	No	Yes	No	No	No
Canadian Association of Medical Oncologists	0 (0)	No	Yes	No	No	No
Canadian Association of Neuropathologists	0 (0)	No	No	No	No	No
Canadian Association of Nuclear Medicine	17 (27)	No	Yes	Yes	No	No
Canadian Association of Paediatric Surgeons	0 (0)	No	Yes	No	No	No
Canadian Association of Pathologists	26 (41)	No	Yes	Yes	Yes	No
Canadian Association of Physical Medicine & Rehabilitation	29 (46)	No	Yes	Yes	Yes	No
Canadian Association of Radiologists	24 (38)	Yes	Yes	Yes	No	No
Canadian Association of Radiation Oncology	0 (0)	Yes	Yes	No	No	No
Canadian Association of	0 (0)	No	No	No	No	No

Thoracic Surgeons						
Canadian Cardiovascular Society	25 (40)	Yes	Yes	Yes	No	No
Canadian College of Medical Geneticists	0 (0)	No	Yes	No	No	No
Canadian Critical Care Society	1 (2)	No	Yes	Yes	No	No
Canadian Dermatology Association	24 (38)	Yes	Yes	Yes	No	No
Canadian Fertility and Andrology Society	23 (37)	Yes	Yes	Yes	No	No
Canadian Geriatrics Society	24 (38)	No	Yes	Yes	No	No
Canadian Heart Rhythm Society	0 (0)	No	Yes	No	No	No
Canadian Hematology Society	0 (0)	No	No	No	No	No
Canadian Neurological Society	25 (40)	Yes	Yes	Yes	Yes	No
Canadian Neurosurgical Society	26 (41)	Yes	Yes	Yes	Yes	No
Canadian Ophthalmological Society	26 (41)	No	Yes	Yes	Yes	No
Canadian Orthopaedic Association	16 (25)	No	Yes	Yes	No	No
Canadian Paediatric Society	19 (30)	Yes	Yes	Yes	Yes	No
Canadian Pain Society	0 (0)	No	Yes	No	No	No
Canadian Psychiatric Association	24 (38)	No	Yes	Yes	Yes	No
Canadian Rheumatology Association	26 (41)	Yes	Yes	Yes	Yes	No
Canadian Society for Clinical Investigation	0 (0)	No	Yes	No	No	No

Canadian Society for Transfusion Medicine	0 (0)	Yes	Yes	No	No	No
Canadian Society for Vascular Surgery	26 (41)	No	Yes	Yes	Yes	No
Canadian Society of Allergy and Clinical Immunology	0 (0)	No	Yes	No	No	No
Canadian Society of Cardiac Surgeons	25 (40)	Yes	Yes	Yes	No	No
Canadian Society of Colon and Rectal Surgeons	0 (0)	No	Yes	No	No	No
Canadian Society of Cytopathology	26 (41)	No	Yes	Yes	Yes	No
Canadian Society of Echocardiography	0 (0)	No	No	No	No	No
Canadian Society of Endocrinology & Metabolism	27 (43)	Yes	Yes	Yes	Yes	No
Canadian Society of Internal Medicine	25 (40)	No	Yes	Yes	Yes	No
Canadian Society of Nephrology	28 (44)	Yes	Yes	Yes	Yes	No
Canadian Society of Otolaryngology — Head & Neck Surgery	22 (35)	Yes	Yes	Yes	No	No
Canadian Society of Palliative Care Physicians	11 (17)	Yes	Yes	Yes	No	No
Canadian Society of Pharmacology and Therapeutics	0 (0)	Yes	No	No	No	No
Canadian Society of Plastic Surgeons	0 (0)	No	Yes	No	No	No
Canadian Society of Surgical Oncology	0 (0)	Yes	No	No	No	No
Canadian Thoracic Society	26 (41)	Yes	Yes	Yes	No	No

Canadian Urological Association	21 (33)	Yes	Yes	Yes	No	No
Occupational Medicine Specialists of Canada	0 (0)	No	No	No	No	No
Public Health Physicians of Canada	0 (0)	No	No	No	No	No
Society of Gynecologic Oncology of Canada	0 (0)	Yes	Yes	No	No	No
Society of Obstetricians and Gynaecologists of Canada	21 (33)	No	Yes	Yes	Yes	No
College of Family Physicians of Canada	33 (52)	No	No	Yes	Yes	No
Royal College of Physicians and Surgeons of Canada	26 (41)	No	Yes	Yes	Yes	No

6.11 APPENDIX 1: POLICY SCORING TOOL FOR CONTINUING MEDICAL EDUCATION (CME) POLICIES ADOPTED BY PROFESSIONAL MEDICAL ASSOCIATIONS (PMAS)

Q1	Does the medical association publicly disclose on its website that it has industry‡ funding generally, unrestricted, or otherwise? Yes/No	
Q2	Does the medical association publicly disclose on its website industry funding specifically for CME activities? Yes/No	
1	Commercial involvement in planning CME activities	
	3	No commercial involvement in planning CME activities is permitted.
	2	If planning of the CME activities includes commercial involvement, the medical organization retains complete control.
	1	Commercial involvement is permitted in planning CME activities and there is no indication that the medical organization retains complete control.
	0	No policy
2	CME committee members' involvement in CME activity planning decisions	
	3	CME committee members must not have any past or present financial ties or relationships with the pharmaceutical industry and this must be disclosed to the committee and publicly on the association's website annually.
	2	CME committee members who have any financial relationships with the pharmaceutical industry should request recusal during meetings in which an area relevant to his or her financial relationships with industry is under consideration.
	1	CME committee members should disclose to the committee any financial relationships with the pharmaceutical industry and may stay in the meeting, but cannot vote in discussions that are relevant to their relationships with industry, or alternative permissive policy.
	0	No policy
3	Presence of a review process for topics of CME activities	
	3	The association has a process in place to review the topics for CME activities. The association is able to request changes to a proposed plan by an external organization or the association can reject activities. The results of this process are publicly available.
	2	The association has a process in place to review the topics for CME activities. The association is able to request changes to a proposed plan by an external organization or the association can reject activities.
	1	The association has a process in place to review the topics for CME activities by an external organization and no other information is provided, or alternative permissive policy.
	0	No policy

‡ "Industry" refers to any commercial, for-profit company including but not limited to pharmaceutical and medical device companies as well as advertising agencies, including medical education communication companies (MECCs) (Steinbrook, 2008), whose purpose is to develop promotional materials often labelled as "educational" or "continuing medical education" (CME) materials that promote their clients' products and services. MECCs may be accredited to provide CME (Relman, 2001).

4	Control over CME activity speakers	
	3	The association has a process in place to review the speakers for CME activities. The association is able to request changes to the proposed speakers or the association can reject the speakers. Speakers with financial conflict of interest relationships within a specified duration of time will not be permitted to speak. The results of this process are publicly available.
	2	The association has a process in place to review the speakers for CME activities. The association is able to request changes to the proposed speakers or the association can reject the speakers.
	1	The association has a process in place to review the speakers for CME activities and no other information is provided, or alternative permissive policy.
	0	No policy.
5	Speakers: Financial conflict of interest disclosures at CME activities	
	3	Speakers must be completely free of financial ties to industry, must not have engaged in financial relationships with industry in the past, and must not have plans to engage in financial relationships with industry in the future. Lack of conflicts must be publicly disclosed during presentations and on the CME activity website.
	2	Past and potential future financial conflict of interest relationships held by speakers must be disclosed on the association's website or at the CME activity. Speakers with present ties to the pharmaceutical industry may not be permitted to speak at the CME activity.
	1	Current financial conflict of interest relationships must be disclosed for speakers during relevant presentations, or alternative permissive policy.
	0	No policy
6	CME committee members and officers: Financial conflict of interest disclosures at CME activities	
	3	CME committee members and officers must be completely free of financial ties to industry, must not have engaged in financial relationships with industry in the past, and must not have plans to engage in financial relationships with industry in the future. Lack of conflicts must be publicly disclosed during presentations and on the CME activity website.
	2	Past and potential future financial conflict of interest relationships held by CME committee members and officers must be disclosed on the association's website or at the CME activity. Involvement of committee members with present ties to the pharmaceutical industry may not be permitted.
	1	Current financial conflict of interest relationships must be disclosed for committee members and officers during relevant presentations, or alternative permissive policy.
	0	No policy
7	Review of educational materials by CME committee Content review for balanced information	
	3	The association has a process in place to review all slides and speaking points to ensure balanced information supported by independent sources. The association can request changes to content to ensure balanced and independent information. The process of peer-review of the content is publicly accessible on the association's website.
	2	The association has a process in place to review all slides and speaking points to ensure balanced information supported by independent sources. The association can request changes to content to ensure balanced and independent information.

	1	Content to be presented at CME events must be submitted to the association before the event, or alternative permissive policy.
	0	No policy
8	Origination of content	
	3	Educational content included in accredited CME is reviewed through a process to ensure that content is developed completely free of sponsors' input regarding how the facilitator, speaker, or writer delivers, covers, revises, and/or edits the educational materials. The process for reviewing the content is publicly accessible on the association's website.
	2	Educational content included in accredited CME is reviewed through a process to ensure that content is developed completely free of sponsors' input regarding how the facilitator, speaker, or writer delivers, covers, revises, and/or edits the educational materials.
	1	It is the responsibility of CME content authors to state how the content was developed, or alternative permissive policy.
	0	No policy
9	Funding for CME activities	
	3	All funding for CME activities comes from registration fees, government funding, funding from the discipline, or other sources that are free of vested interests.
	2	Funding for CME activities comes from a mixture of non-commercial and commercial sources but no one company is permitted to supply the majority of the funding to individual CME activities or events.
	1	Funding for CME activities comes from a mixture of non-commercial and commercial sources and one company is permitted to supply the majority of the funding to individual CME activities or events, or all funding for individual CME events can come from commercial sources or alternative permissive policy.
	0	No policy
10	Disclosure and transparency of funding for CME activities	
	3	All funding information (i.e., how funds are used for CME), the names of sponsors, and amounts donated by each to the association are publicly accessible on the association's website when registration for the event begins.
	2	Funding information (i.e., how funds are used for CME) and the names of sponsors are publicly accessible on the association's website when registration for the CME event begins.
	1	The names of CME sponsors are publicly accessible at the time of the event on the association's website, or alternative permissive policy.
	0	No policy
11	Responsibility for distribution of funds	
	3	The CME committee is responsible for distributing restricted and unrestricted grants from industry. The distribution of funds is publicly accessible.
	2	The CME committee is responsible for distributing restricted and unrestricted grants from industry.
	1	The CME committee, in consultation or with the involvement of commercial industry, distributes restricted and unrestricted grants from industry, or alternative policy.
	0	No policy
12	Awards	
	3	Awards (e.g., best original research, best poster at CME event) presented at the association's CME activities must not be industry sponsored and must not bear the name of CME event industry sponsors.

	2	Awards (e.g., best original research, best poster at CME event) may be industry-sponsored, but must not bear the name of the industry sponsors.
	1	Awards (e.g., best original research, best poster at CME event) may be industry-sponsored and may bear the name of the industry sponsors, or no indication that these are prohibited, or alternative permissive policy.
	0	No policy
13	Industry personnel, representatives, and employees	
	3	Industry personnel, representatives, and employees are not permitted in the CME activity areas that are association-designated "educational" or "social" areas. If industry employees pay to attend the CME event, their nametags must identify them as "Industry employee" or "Industry representative", but must not state the company that they are from. They are not permitted to promote their products or services in any area.
	2	Industry personnel, representatives, and employees are not permitted in CME activity areas that are association-designated as "educational" or "social" and are only permitted in association-designated "marketing" areas.
	1	Industry personnel, representatives, and employees are permitted in "social" and "educational" areas, but are not permitted to promote their products or services in those areas, or alternative permissive policy.
	0	No policy
14	Distribution of industry-funded educational materials at CME activities	
	3	The association does not allow any industry-originated educational materials to be distributed at the association's CME activities or materials distributed must be developed completely independently of industry or sponsoring organizations.
	2	The association allows some pre-reviewed industry-originated or funded educational materials to be distributed at the CME event, but makes it known to the attendees that it does not endorse these materials.
	1	The association allows the distribution of some industry-originated or funded educational materials at the CME event, or alternative permissive policy.
	0	No policy
15	Distinction between marketing and educational materials	
	3	The association has established a mechanism by which CME attendees are informed of whether the association considers the content to be "educational" or "marketing". The description of the mechanism is publicly accessible on the association's website.
	2	The association has established a mechanism by which CME attendees are informed of whether the association considers the content to be "educational" or "marketing".
	1	The association allows both educational and marketing material to be distributed by companies at CME events without a mechanism to distinguish between the two, or alternative permissive policy.
	0	No policy
16	Branded items	
	3	Branded items are prohibited from the association's CME activities. No company logos are to appear on educational materials, tote bags, lanyards, pens, notebooks, and publications distributed to members at any CME activities. Attendees and company representatives may not wear or display branded items in education-designated areas.

	2	Branded items are prohibited from the association's CME activities. No company logos are to appear on educational materials, tote bags, lanyards, pens, notebooks, and publications distributed to members at educational sessions at CME events.
	1	Branded items are permitted to be printed on educational materials or given to attendees in certain areas designated for marketing or promotional activity, or alternative permissive policy.
	0	No policy
17	Exhibit halls and booths	
	3	No exhibit hall space or booths are to be sold to pharmaceutical companies at the association's CME event.
	2	Exhibit halls are explicitly defined as marketing spaces to attendees. The association is permitted to sell exhibit hall space to companies, provided that it is defined and visibly designated as an industry-sponsored advertising space that is physically separate from and not intermixed with non-industry sponsored educational material presentation space. Industry-sponsored booths are prohibited from being located in the obligate path to a scientific or educational session and must be clearly delineated so that attendees understand that they are entering a marketing site.
	1	The association is permitted to sell exhibit hall space to companies, provided that it is clearly labelled as an advertising space to attendees, or alternative permissive policy.
	0	No policy
18	Use of brand or trade names	
	3	CME activities must not, at any stage of CME development, either directly or indirectly endorse any particular products and may not use brand or trade names of drugs, unless it is essential that the brand name be used (i.e., if warning about a particular harm of a specific brand name drug, and the generic name must accompany the brand name in this warning).
	2	CME activities must not, at any stage of CME development, either directly or indirectly endorse any particular products and may not use brand or trade names of drugs. Should CME activities name a brand or trade name of a drug, it must be used only once and all other products in the same drug class must also be named and granted equal prominence within the specific activity.
	1	CME activities should avoid using brand or trade names of drugs, or alternative permissive policy.
	0	No policy
19	Promotion of unapproved uses or off-label indications	
	3	Any presentation on or including unapproved uses or off-label indications of medications in accredited CME activities is prohibited.
	2	Any presentation on or including unapproved uses or off-label indications of medications in accredited CME activities is permitted as long as speakers inform the audience that these uses are not approved.
	1	Presenting on unapproved uses or off-label indications of medications in accredited CME is permitted, or alternative permissive policy.
	0	No policy
20	Sharing attendee information	
	3	The association does not share participant, member, or attendee demographic information, including names, addresses, email addresses, and any contact information at any time with any pharmaceutical company.

	2	The association has developed specific criteria that outline the conditions under which it will share participant, member, or attendee demographic information, including names, email addresses, and any contact information with pharmaceutical companies. Individuals may opt out of having their information shared.
	1	The association has developed specific criteria that outline the conditions under which it will share participant, member, or attendee demographic information, including names, addresses, email addresses, and any contact information with pharmaceutical companies, or alternative permissive policy.
	0	No policy
21	Satellite symposia	
	3	The association does not endorse satellite symposia, or allow publicity for them at the association's CME events.
	2	The association does not endorse satellite symposia, but may allow publicity for them at the association's CME events.
	1	The association may endorse satellite symposia and may allow for publicity for them at the association's events, or alternative permissive policy.
	0	No policy
E	Enforcement of CME-related policy/section of policy	
EA	Is it clear within the policy that there is a party responsible for general oversight to ensure compliance? (Y/N)	
EB	Is it clear within the policy that there are sanctions for noncompliance? (Y/N)	
EC	Is it clear within the policy that the results of investigations into noncompliance will be publicly accessible on the association's website? (Y/N)	

6.12 APPENDIX 2: SUMMARY OF POLICIES AND DATES OF MOST RECENT REVIEW OR ADOPTION FOR 60 CANADIAN PROFESSIONAL MEDICAL ASSOCIATIONS BETWEEN 2004 AND 2015

60 Canadian Professional Medical Organizations		Name of policy	Date of adoption or most recent review
1	Association of Medical Microbiology and Infectious Disease Canada	no specific policies	n/a
2	Canadian Academy of Child and Adolescent Psychiatry	no specific policies	n/a
3	Canadian Academy of Geriatric Psychiatry	no specific policies	n/a
4	Canadian Academy of Psychiatry and the Law	Disclosure form	No date
5	Canadian Academy of Sport and Exercise Medicine	no specific policies	n/a
6	Canadian Anesthesiologists' Society	CMA policy: Guidelines for physicians in interactions with industry	May 2012
		Approval process for a continuing professional development activity for RCPSCP section 1 credits (accredited group learning activities) not-for-profit non-accredited physician organization	May 2012
		Relationships with industry sponsors and for-profit physician groups/organizations in continuing professional development activities	May 2012
		Approval process for a continuing professional development activity for RCPSCP section 1 credits (accredited group learning activities) co-development with non-physician organizations	May 2012
		CAS relationships with industry for accredited CPD activities	No date
		Declaration	May 2012
7	Canadian Association of Emergency Physicians	CAEP endorsement guidelines	November 2014
		CAEP policies on the development of roadshows	June 4, 2006

		Procedures – roadshow development	June 4, 2006
8	Canadian Association of Gastroenterology	Industry interaction policy	July 24, 2008
		CAG policy on the dissemination of CAG material	July 3, 2008
		Policy for the publication of educational symposia/events proceedings by the CAG and industry	June 2, 2008
		CMA policy: Guidelines for physicians in interactions with industry	2007
		MOC guidelines	Page not found
		Accreditation	Page not found
9	Canadian Association of General Surgeons	Self-assessment program (SAP) (section 3) application form	No date
		Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	2010
		CMA policy: guidelines for physicians in interactions with industry	2007
		Accreditation application manual: Approval process, policy and procedure for section 1 and section 3 program applications	No date
10	Canadian Association of Interventional Cardiology	no specific policies	n/a
11	Canadian Association of Medical Biochemists	no specific policies	n/a
12	Canadian Association of Medical Oncologists	no specific policies	n/a
13	Canadian Association of Neuropathologists	no specific policies	n/a
14	Canadian Association of Nuclear Medicine	Policies and procedures relating to the review of programs submitted for approval under section 3	September 2013
		Policies and procedures relating to the review of CPD events submitted for approval under section 1	September 2013
		CMA policy: Guidelines for physicians in interactions with industry	2007

15	Canadian Association of Paediatric Surgeons	no specific policies	n/a
16	Canadian Association of Pathologists	CPD event & program accreditation	No date
		Declaration of conflicts of interest	No date
		CMA policy: Guidelines for physicians in interactions with industry	2007
		CAP-ACP Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of MOC program	March 2015
		Information for workshop directors	No date
17	Canadian Association of Physical Medicine & Rehabilitation	Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	2014
		Conflict of interest	February 2, 2004
		Accreditation application manual: Approval process including policies and procedures MOC program	December 2013
		Guidelines for relationships with sponsors	July 2006
		Relationships with speakers and/or financial sponsors	No date
		Self-assessment program (SAP) application form: Approval of accredited self-assessment Section 3 of the framework of CPD options of the MOC program	December 2013
		Accredited simulation activities application form: Approval of accredited simulation activities within Section 3 of the framework of CPD options of the MOC program	December 2013
		Guidelines and process for accreditation of a non-physician organization activity	December 2013
		Guidelines and process for accreditation of a co-developed physician organization activity	December 2013
		Declaration of conflict of interest	No date
18	Canadian Association of Radiologists	Accreditation of specialist programming group learning activities	November 2013

		Accreditation application form Section 3 self-assessment program	No date
		CMA policy: guidelines on physicians in interactions with industry	2007
		Accredited self-assessment programs section 3 of RCPSC maintenance of certification program	August 2008
19	Canadian Association of Radiation Oncology	no specific policies	n/a
20	Canadian Association of Thoracic Surgeons	no specific policies	n/a
21	Canadian Cardiovascular Society	CMA policy: guidelines for physicians in interactions with industry	2007
		External relations policy	2012
		The role and responsibilities of the chair of a planning committee	No date
		CCS accreditation: MOC section 1 educational activities: Policies procedures and application form	March 2015
		A handbook for planning committees developing educational programs	October 23, 2012
		Faculty presentation checklist	No date
		Disclosure of potential conflict of interest	No date
		Section 1 accreditation request form	No date
22	Canadian College of Medical Geneticists	no specific policies	n/a
23	Canadian Critical Care Society	no specific policies	n/a
24	Canadian Dermatology Association	Policy on faculty disclosure of potential conflicts of interest and off-label use	No date
		Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	2010
		CMA policy: guidelines for physicians in interactions with industry	2007
		Self-assessment program (SAP) application: Section 3 of the framework of CPD options of the MOC program	2010
25	Canadian Fertility and Andrology Society	CMA policy: Guidelines for physicians in interactions with industry	2007

		Continuing professional development committee	July 1, 2011
		Ethical standards disclosure	No date
		Self-approval requirements for rounds, journal clubs or other hospital-based educational events	No date
		Self-approval requirements for small group learning activities	No date
		MOC accreditation application: approval of section 1 accredited group learning activities of the framework of CPD options of the MOC program	No date
		MOC application for accredited self-assessment programs for approval of section 3 accredited learning activity of the framework of CPD options of the MOC program	No date
		The Royal College of Physicians and Surgeons of Canada: CPD program guide	May 2006
26	Canadian Geriatrics Society	CMA policy: Guidelines for physicians in interactions with industry	2007
		Accreditation application manual: approval process including policies and procedures	January 29, 2014
27	Canadian Heart Rhythm Society	no specific policies	n/a
28	Canadian Hematology Society	no specific policies	n/a
29	Canadian Neurological Society	Lunch 'n learn guidelines	No date
		Disclosure of conflict of interest	No date
		Relationships with speakers and/or financial sponsors	No date
		Guidelines and process for physician organizations: application process for activities developed by physicians organizations for MOC section 1 credits	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
		Disclosure form	No date
		Guidelines and process for co-development with an accredited provider	No date

		Standards for accredited simulation activities (section 3)	2013
		Standards for accredited self-assessment programs (section 3)	2010
		Self-assessment program (SAP) application form: Approval of accredited self-assessment programs Section 3 of the framework for CPD options of MOC program	2014
		Application form for MOC section 1 accredited group learning activities CNSF congress co-developed symposium	October 2015
30	Canadian Neurosurgical Society	Lunch 'n learn guidelines	No date
		Disclosure of conflict of interest	No date
		Relationships with speakers and/or financial sponsors	No date
		Guidelines and process for physician organizations: application process for activities developed by physicians organizations for MOC section 1 credits	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
		Disclosure form	No date
		Guidelines and process for co-development with an accredited provider	No date
		Self-assessment program (SAP) application form: Approval of accredited self-assessment programs Section 3 of the framework for CPD options of MOC program	2014
		Standards for accredited simulation activities (section 3)	2013
		Standards for accredited self-assessment programs (section 3)	2010
		Application form for MOC section 1 accredited group learning activities CNSF congress co-developed symposium	October 2015
31	Canadian Ophthalmological Society	Accreditation guide: continuing professional development activities developed by physician organizations	December 22, 2014

		Application form for accreditation of a CPD event developed by a physician organization	No date
		COS conflict of interest disclosure form	No date
		Application form for accreditation of a co-developed CPD event	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
32	Canadian Orthopaedic Association	Application form: approval of accredited group learning activities: section 1 of the framework of CPD options of the maintenance of certification program	March 2013
		Royal College maintenance of certification program	Link broken
33	Canadian Paediatric Society	Maintenance of certification group learning application form (for physician organizations) section 1 of the framework of CPD options of the MOC program	February 2013
		Sponsorship	January 2, 2008
		Section 3 - self assessment programs	August 27, 2015
		Accrediting your education activity	November 19, 2014
		Guidelines for CPS co-development of section 1 accredited group learning activities with non-physician organizations	October 2014
		Maintenance of certification self-assessment program (SAP) application form section 3 of the framework for CPD options of the MOC	August 2015
		Disclosure of potential conflict of interest	Link broken
		A guide for accreditation of continuing medical education	October 22, 2014
34	Canadian Pain Society	no specific policies	n/a
35	Canadian Psychiatric Association	Self-assessment program (SAP) application form: Approval of accredited self-assessment programs: Section 3 of the MOC program	2010
		Continuing professional development mission statement	No date

		Criteria for section 1 approval: Approval of accredited group learning activities MOC program physician organizations	November 2014
		Disclosure of conflict of interest	No date
		Requirements for CPA co-developed programs	No date
		Self-assessment program s (section 3)	No date
		CMA policy: Guidelines for physicians in interactions with industry	2007
		Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	2014
		Application form for approval of Section 1 accredited group learning activities MOC program	November 2014
		Relationships with speakers and/or financial sponsors	No date
36	Canadian Rheumatology Association	CRA industry council guidelines	No date
		CRA application form for MOC approval: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	May 2015
		Procedures for section 1 and co-developed applications under the MOC program	November 2014
		Declaration of conflict of interest	No date
		Disclosure of conflict of interest	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
		Co-development checklist	May 28, 2014
		Guidelines and process for co-development with an accredited provider	No date
		Guidelines and process for physician organization	No date
		Guidelines and process for co-development with a non-accredited physician organization	No date
		Relationships with speakers and/or financial sponsors	No date

		Standards for accredited simulation activities (section 3)	2013
37	Canadian Society for Clinical Investigation	no specific policies	n/a
38	Canadian Society for Transfusion Medicine	no specific policies	n/a
39	Canadian Society for Vascular Surgery	CSVS continued professional development MOC	No date
		Disclosure of conflict of interest	No date
		Declaration of conflict of interest	No date
		Guidelines and process for physician organization	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
		Guidelines and process for co-development with an accredited provider	No date
		Guidelines and process for co-development with a non-accredited physician organization	No date
		Guidelines for approval of CPD activities developed by a physician organization - section 1	No date
		CSVS application form for MOC approval: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	January 2011
		Relationships with speakers and/or financial sponsors	No date
40	Canadian Society of Allergy and Clinical Immunology	no specific policies	n/a
41	Canadian Society of Cardiac Surgeons	CMA policy: guidelines for physicians in interactions with industry	2007
		External relations policy	2012
		The role and responsibilities of the chair of a planning committee	No date
		CCS accreditation: MOC section 1 educational activities: Policies procedures and application form	March 2015
		A handbook for planning committees developing educational programs	October 23, 2012
		Faculty presentation checklist	No date
		Disclosure of potential conflict of interest	No date

		Section 1 accreditation request form	No date
42	Canadian Society of Colon and Rectal Surgeons	Sponsorship	No date
43	Canadian Society of Cytopathology	CPD event & program accreditation	No date
		Declaration of conflicts of interest	No date
		Information for workshop directors	No date
		CAP-ACP Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of MOC program	March 2015
		CMA policy: Guidelines for physicians in interactions with industry	2007
44	Canadian Society of Echocardiography	no specific policies	n/a
45	Canadian Society of Endocrinology & Metabolism	Guidelines and processes for accredited events for physician organizations	No date
		Guidelines and processes for accredited events for non-physician organizations	No date
		Application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	No date
		Disclosure of conflict of interest	No date
		Declaration of conflict of interest	No date
		Accreditation for co-developed symposia at the annual meeting	No date
		CPD disclosure form: Planning committee member/speaker/moderator/facilitator	No date
		CPD section 1 application fee structure	No date
		Relationships with speakers and/or financial sponsors	No date
		Guidelines and process for physician organizations	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
		Guidelines and processes for co-development with an accredited provider	No date

		Guideline and process for co-development with a non-accredited physician organization	No date
46	Canadian Society of Internal Medicine	CME/CPD mission statement	No date
		CSIM application form for MOC approval: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	August 17, 2015
		Self-assessment program (SAP) application form: Approval of accredited self-assessment programs section 3 of the framework of continuing professional development (CPD) options of the maintenance of certification program	December 2014
		CMA policy: guidelines for physicians in interactions with industry	2007
		The role of the Canadian Society of Internal Medicine in the approval and co-development of CPD activities	November 6, 2014
		Disclosure of conflict of interest	No date
		Relationships with speakers and/or financial sponsors	No date
		Guidelines and process for physician organizations	No date
		Guidelines and process for co-development with an accredited provider	No date
		Guideline and process for co-development with a non-accredited physician organization	No date
47	Canadian Society of Nephrology	Canadian Society of Nephrology guidelines for development and accreditation of educational activities	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
		Conflict of interest and disclosure policy for the Canadian Society of Nephrology	No date
		Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of continuing professional development (CPD) options of the MOC program	No date

		Self-assessment program (SAP) application form: Approval of accredited self-assessment programs: Section 3 of the framework of CPD options of the MOC program	No date
		Conflict of interest policy	No date
		Basic conflict of interest disclosure form	No date
48	Canadian Society of Otolaryngology — Head & Neck Surgery	Group learning application form: Approval of accredited group learning activities: Section 1 of the framework of continuing professional development (CPD) options of the MOC program	2010
		CMA policy: guidelines for physicians in interactions with industry	2007
		Policies and procedures for co-development of CDP activities with physician and non-physician organizations	June 2010
		Section 1 application form	Page not found
		Accreditation toolkit	Page not found
49	Canadian Society of Palliative Care Physicians	Policy pertaining to donors, exhibitors, sponsors, and advertisers	November 2, 2014
		Policy on relationship with industry	October 17, 2009
50	Canadian Society of Pharmacology and Therapeutics	no specific policies	n/a
51	Canadian Society of Plastic Surgeons	no specific policies	n/a
52	Canadian Society of Surgical Oncology	no specific policies	n/a
53	Canadian Thoracic Society	Application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	2012
		CMA policy: Guidelines for physicians in interactions with industry	Link broken
		Policy and procedures regarding co-development of educational programs	May 12, 2014
		Summary of requirements for accreditation	No date

54	Canadian Urological Association	2015 policy book	June 29, 2015
		CUA declaration of potential conflict of interest form	No date
		Speaker checklist	No date
		Application form: Approval of accredited group learning activities: Section 1 of the framework of CPD options of the MOC program	February 2007
		CUA accreditation policy for physician organizations	No date
55	Occupational Medicine Specialists of Canada	no specific policies	n/a
56	Public Health Physicians of Canada	no specific policies	n/a
57	Society of Gynecologic Oncology of Canada	no specific policies	n/a
58	Society of Obstetricians and Gynaecologists of Canada	Accreditation	No date
		Conflict of interest policy statement	Password protected
		A handbook for planning committees developing educational programs	No date
		SOGC accreditation: MOC section 1 educational activities policies, procedures and application form physician and non-physician organizations	No date
		Disclosure of potential conflict of interest form	No date
59	College of Family Physicians of Canada	Conflict of interest form	No date
		Declaration of conflict of interest	June 1, 2012
		Establishing limits on meal expenses related to Mainpro-accredited events	No date
		A guide to Mainpro accreditation	2014
		Ethical review and guidelines	No date
		Ethical review form	November 10, 2015
		Quick tips: Identification and management of conflicts of interest and transparency to learners	No date
		CMA policy: guidelines for physicians in interactions with industry	2007
60	Royal College of Physicians and Surgeons of Canada	Accredit rounds, journal clubs and small groups	No date

		Accreditation of simulation programs	No date
		Accreditation committee	October 2013
		Accreditation standards for a journal club	No date
		Accreditation standards for rounds or other hospital-based educational activities	No date
		Accreditation standards for a small group	No date
		Disclosure of conflict of interest	No date
		Continuing professional development (CPD) accreditation committee	May 23, 2013
		CPD activity grant	No date
		Continuing professional development (CPD) activity grant: Guidelines and application form	November 2014
		Criteria for approval of online CPD events for MOC	No date
		Education committee	June 17-18, 2013
		Education research development committee	May 13, 2015
		Evaluation of CPD group activities	2012
		Guidelines and process for physician organizations	No date
		Guidelines and process for co-development with an accredited provider	No date
		Guidelines and process for co-development with a non-accredited physician organization	No date
		International agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association	January 1, 2013
		CMA policy: Guidelines for physicians in interactions with industry	2007
		Professional development committee	May 23, 2013
		Relationships with speakers and/or financial sponsors	No date
		Renewal of previously approved SAP application form: Section 3 of the	August 2008

		framework of CPD options of the MOC program	
		Royal College accreditation standards for accredited CPD provider organizations	No date
		Accredited simulation activities application form: Approval of accredited simulation activities within Section 3 of the framework for CPD options of the MOC program	November 10, 2014
		Standards for accredited self-assessment programs (Section 3)	2010
		Standards for accredited simulation activities (Section 3)	2013
		Group learning application form: Approval of accredited self-assessment programs: Section 1 of the framework of CPD options of the MOC program	2014
		Self-assessment program (SAP) application form: Approval of accredited self-assessment programs: Section 3 of the framework of CPD options of the MOC program	2014
		Self-assessment program checklist	February 2012

INTEGRATIVE DISCUSSION

An important role of Canadian professional medical associations (PMAs) is the provision of accredited continuing medical education (CME) programs for their physician members. Because accredited CME programs have received funding from commercial industry, it is important to evaluate the degree to which Canadian medical associations permit or prohibit industry involvement in these programs. The study on policies concerning accredited CME adopted by 60 Canadian PMAs (Chapter 6) found that the associations generally had nonexistent, permissive, or moderately restrictive policies. The categories that received the highest average scores were commercial involvement in planning CME activities, the presence of a review process for CME program topics, content review for balanced information, and responsibility of distribution of funds. The lowest average scores were received in the areas of awards, industry personnel, representatives and employees, distribution of industry-funded educational materials at CME activities, and distinction between marketing and educational materials. None of the categories received a score of 3, which would have indicated that industry involvement is prohibited. Furthermore, the majority of PMAs disclosed having received industry sponsorship for CME events in the last five years. Therefore, there are opportunities for not only industry sponsorship, but also industry involvement in the planning, logistics, and content choice of CME programs that are accredited by Canadian professional medical associations.

In addition to hosting accredited CME programs for physicians, professional medical associations also widely distribute clinical practice guidelines (CPGs) to

physicians. Clinical practice guidelines are considered to be authoritative guidance documents that are meant to inform physicians' treatment decisions for their patients. Although these guidelines should be based on the best available clinical evidence, recommendations have been based on lower levels of evidence or expert opinion. The decisions about the evidence on which to base recommendations in CPGs may be vulnerable to bias, since guideline authors and guideline development committee members may have financial conflict of interest (FCOI) relationships with the pharmaceutical industry. The next manuscript (Chapter 7) presents an analysis of FCOI relationship disclosures made by authors on Canadian clinical practice guidelines, which were obtained from the Canadian Medical Association Infobase.

CHAPTER 7

REPORTING OF FINANCIAL CONFLICTS OF INTEREST IN CLINICAL PRACTICE GUIDELINES: A CASE STUDY ANALYSIS OF GUIDELINES FROM THE CANADIAN MEDICAL ASSOCIATION INFOBASE

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7.1 SUMMARY

Background

Clinical practice guidelines are widely distributed by medical associations and relied upon by physicians for the best available clinical evidence. International findings report that financial conflicts of interest (FCOI) with drug companies may influence drug recommendations and are common among guideline authors. There is no comparable study on exclusively Canadian guidelines; therefore, we provide a case study of authors' FCOI declarations in guidelines from the Canadian Medical Association (CMA) Infobase. We also assess the financial relationships between guideline-affiliated organizations and drug companies.

Methods

Using a population approach, we extracted first-line drug recommendations and authors' FCOI disclosures in guidelines from the CMA Infobase. We contacted the corresponding authors on guidelines when FCOI disclosures were missing for some or all authors. We also extracted guideline-affiliated organizations and searched each of their websites to determine if they had financial relationships with drug companies.

Results

We analyzed 350 authors from 28 guidelines. Authors were named on one, two, or three guidelines, yielding 400 FCOI statements. In 75.0% of guidelines at least one author, and in 21.4% of guidelines all authors, disclosed FCOI with drug companies. In 54.0% of guidelines at least one author, and in 28.6% of guidelines over half of the authors,

disclosed FCOI with manufacturers of drugs that they recommended. Twenty of 48 authors on multiple guidelines reported different FCOI in their disclosures. Eight guidelines identified affiliated organizations with financial relationships with manufacturers of drugs recommended in those guidelines.

Conclusions

This is the first study to systematically describe FCOI disclosures by authors of Canadian guidelines and financial relationships between guideline-affiliated organizations and pharmaceutical companies. These financial relationships are common. Because authoritative value is assigned to guidelines distributed by medical associations, we encourage them to develop formal policies to limit the potential influence of FCOI on guideline recommendations.

KEYWORDS

Financial conflicts of interest, disclosure, clinical practice guidelines, medicine and the pharmaceutical industry, treatment recommendations

7.2 BACKGROUND

Clinicians rely on clinical practice guidelines (CPGs) for guidance when making treatment decisions for patients. Although CPGs should be based on critical analysis of the best available scientific evidence, authors' recommendations in some guidelines have been based on lower levels of evidence or expert opinion (Tricoci, Allen, Kramer, Califf, & Smith, 2009). Therefore, recommendations may be vulnerable to biases (Brix Bindslev, Schroll, Gotzsche, & Lundh, 2013), which are of particular concern since financial ties are common among guideline authors, committee members, and drug companies that manufacture medications recommended in guidelines (Abramson & Starfield, 2005). A common finding in the literature analyzing guideline recommendations is that the presence of financial conflict of interest (FCOI) relationships with pharmaceutical companies may have the potential to influence drug recommendations (Bekelman, Li, & Gross, 2003; Bero, Oostvogel, Bacchetti, & Lee, 2007; Cosgrove, Bursztajn, Krimsky, Anaya, & Walker, 2009; DeAngelis & Fontanarosa, 2008; Kelly et al., 2006; Lexchin, 2008; Lundh, Sismondo, Lexchin, Busuioc, & Bero, 2012; Perlis, Harwood, & Perlis, 2005; Rochon et al., 1994; Sismondo, 2008). Furthermore, international literature has demonstrated concern over underreporting and inconsistencies in FCOI disclosures in guidelines (Abramson & Starfield, 2005; Brix Bindslev et al., 2013; Choudhry, Stelfox, & Detsky, 2002; Guyatt et al., 2010; Norris, Holmer, Ogden, & Burda, 2011; Norris, Holmer, Ogden, Burda, & Fu, 2013).

CPGs are widely distributed by professional medical associations, such as the Canadian Medical Association (CMA). The CMA Infobase (https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx) lists guidelines that meet the following criteria: include information to help patients and physicians make decisions about appropriate health care for specific clinical circumstances; be produced by an authoritative Canadian organization or if produced outside of Canada be officially endorsed by such an organization; have been developed or reviewed in the last 5 years; and have evidence that a literature search was performed during guideline development (Canadian Medical Association [CMA], 2015).

We present a case study of authors' FCOI disclosure statements in guidelines from the CMA Infobase. We determine the prevalence of not only authors' disclosed FCOI with drug companies in general, but also their FCOI disclosures with the manufacturers of the on-patent drugs that they recommend as first-line treatments in their respective guidelines. Our focus on on-patent drugs rests on the assumption that recommending an on-patent drug is directly beneficial to a single manufacturer, as compared to recommending an off-patent drug, produced by multiple manufacturers. Finally, we determine the frequency with which the guideline-affiliated organizations have financial relationships with pharmaceutical companies that are also manufacturers of the drugs recommended as first-line treatments in those guidelines.

7.3 METHODS

Using a population approach, we analyzed 1,150 guidelines listed in the CMA Infobase. We did not limit our case study of guidelines by medical specialty or disease

category; however, we limited the eligible guidelines to the 353 listed on the CMA Infobase (Canadian Medical Association (CMA), 2014) that were published or most recently reviewed between 01 January 2012 and 06 November 2013, inclusive. We imposed this date restriction because the requirement for FCOI disclosure is a relatively recent phenomenon in guideline production (Mendelson, Meltzer, Campbell, Caplan, & Kirkpatrick, 2011). French-language guidelines and those that could not be accessed on the web were excluded.

Two pairs of study researchers (AS and MR, JL and SA) assessed and documented whether guidelines recommended specific drugs based on recommendation tables or, in their absence, within the text. We considered a "recommendation" to have been made when authors stated that one or more specific medications were appropriate first-line treatments for a particular patient population. We excluded guidelines that either recommended only drug classes as opposed to specific medications, or mentioned or acknowledged specific drugs without making clear first-line recommendations (Figure 7.1).

Specific drugs for first-line treatment were recommended in 102 guidelines. Guidelines that provided only titles of organizations, committees, or associations in lieu of individually named authors or committee members were excluded, leaving 77 guidelines. Forty additional guidelines that provided neither disclosures, nor corresponding authors' contact information were excluded (Figure 7.1). Any disagreements or uncertainties were resolved through discussion.

From the remaining 37 guidelines, we attempted to locate disclosure statements for the authors. Twenty guidelines provided FCOI disclosure statements for all or some

of the authors named on the guideline. Disclosure statements were absent in 10 guidelines and seven guidelines provided links to FCOI disclosure statements on external websites. We successfully accessed five of these external webpages (Figure 7.2). We contacted the corresponding authors on 15 guidelines for one of two reasons: (1) the guideline had no FCOI disclosure section and there was no indication that all authors were either free of FCOI or had any conflicts to report (10 guidelines), or (2) disclosures were either vague, or missing for some authors and the guideline did not state that these authors were free of FCOI (5 guidelines). We received responses from 11 of the 15 corresponding authors whom we contacted, but only five provided us with additional FCOI disclosure statements.

Ultimately, we located FCOI disclosures for all of the authors on 22 guidelines and some authors on 6 guidelines yielding 350 unique authors, of whom 48 were named on two or three guidelines, resulting in a total of 400 disclosure statements. We divided FCOI disclosures with pharmaceutical companies into two groups – relevant and non-relevant. We considered FCOI to be "relevant" when they existed between an author and the manufacturer of a patented drug recommended for first-line treatment in that guideline. "Non-relevant" FCOI were those with a drug company other than the manufacturer of one of the recommended drugs (Norris et al., 2013). These companies may have produced a drug that could also be used to treat the condition being discussed in the guideline but they may also have produced a drug that was not useful for the condition. We did not attempt to distinguish between the two situations as that would have involved analyzing every drug made by the company and then using expert opinion to decide if one (or more) of these drugs could have been recommended.

We considered FCOI to include not only financial compensation, but also activities that are generally associated with gifting, payment, or reimbursement, even if a monetary value was not disclosed. We defined "vague" FCOI disclosures as situations when financial ties were present, but the declaration prevented a clear determination of the number of pharmaceutical companies with which authors held FCOI and whether those FCOI could be classified as relevant or non-relevant. Conflicts with "non-commercial" organizations were defined as ties that authors disclosed with not-for-profit organizations such as the Canadian Agency for Drugs and Technologies in Health (CADTH).

Because of resource limitations, we decided *a priori* to extract FCOI disclosure information for a maximum of 25 authors per guideline, including chairs, co-chairs, principle authors, co-authors, and committee members. We assumed that all committee members who were named within the guideline had voted on its recommendations, even if they were not explicitly listed as authors. We also assumed that anyone who was not identified as an author or named committee member (i.e., reviewers, consultants, and liaisons) did not vote on the final recommendations in the guidelines and we excluded them. When more than 25 authors and/or committee members, which will hereafter be referred to collectively as authors, were named on a guideline, we assigned each a random value using Microsoft Excel (Microsoft, 2013). Organized in ascending numerical order, the top 25, automatically including explicitly identified chair(s), co-chair(s), and principal author(s), were included in our analysis. We included these groups because we considered that they had the most influence in the final recommendations and, therefore, the presence or absence of their FCOI was particularly important. However, due to their

small numbers we did not analyze chairs, co-chairs and principal authors separately. We also extracted authors' demographic information from the guidelines: names, academic and medical degrees, and hospital and academic affiliations.

We recorded whether the medications recommended in the guidelines were on-patent or if there were off-patent versions available in Canada by consulting the Compendium of Pharmaceuticals and Specialties (CPS) and Health Canada's Drug Products Database (Canadian Pharmacists Association (CPA), 2012, 2013; Health Canada, 2013) for the years that the guidelines were either published or reviewed to determine whether authors' FCOI declarations were relevant or non-relevant.

Finally, we identified the guideline-affiliated organizations. We visited each of the organizations' websites to identify the pharmaceutical companies with which they disclosed having financial relationships. We did not examine whether conferences held by these organizations had pharmaceutical company sponsors.

This study has received ethics approval from the Ethics Review Board at York University and conforms to the standards of the Tri-Council Research Ethics guidelines (Certificate #: 2014 - 186). Written informed consent for participation in this study was obtained from participants.

7.4 RESULTS

We obtained FCOI disclosures for authors on 28 guidelines. Twelve were most recently reviewed or published in 2013 and 16 in 2012.

Out of 400 FCOI disclosure statements for 350 unique authors, 188 (47.0%) declared FCOI with pharmaceutical companies. Individual authors declared FCOI with up to 19 drug companies (median: 3, interquartile range [IQR]: 0, 8). Out of these 188 FCOI declarations, 97 were relevant, 65 were non-relevant, and 26 were vague. Two-hundred and twelve (53.0%) of the 400 declarations stated that the authors were either free of FCOI with drug companies or had conflicts with only non-commercial organizations (Table 7.1).

7.4.1 Author-level analysis

Three-hundred and two unique authors (86.3%) were each on one guideline, while 46 (13.1%) were each on two guidelines and two (0.6%) were each on three guidelines. Of the authors on one guideline, 119 (34.0%) disclosed FCOI with drug companies, while 162 (46.3%) disclosed that they had either conflicts with non-commercial organizations or were free of FCOI with drug companies. Twenty-one (6.0%) disclosed vague FCOI with drug companies (Table 7.2).

Twenty-eight of the 48 authors' declarations on two or three guidelines were consistent in their disclosure statements, but 20 disclosed different FCOI in their disclosure statements in two or three guidelines. Authors whose disclosures differed in their multiple statements declared a combination of the following disclosure types: FCOI with different drug companies, vague FCOI with drug companies, conflicts with only non-commercial organizations, and no FCOI (Table 7.2).

7.4.2 Guideline-level analysis

In twenty-one guidelines (75.0%) at least one author disclosed FCOI with drug companies, while in six guidelines (21.4%) all authors disclosed FCOI with drug companies (median: 69.4%, IQR: 3.0%, 93.1%) (Table 1). In fifteen guidelines (54.0%) at least one author disclosed relevant FCOI (median: 6.5%, IQR: 0%, 66.7%), while in one guideline (3.6%) all authors disclosed relevant FCOI. In eight guidelines (28.6%), over half of the authors declared relevant FCOI (Table 7.1).

The majority of guidelines identified affiliations with organizations (26/28, 93.0%). In total, 39 organizations were found. Nineteen of the 39 organizations (49.0%) identified financial relationships with pharmaceutical companies on their respective websites. In eight guidelines (26.0%), at least one drug recommended for first-line treatment was manufactured by a pharmaceutical company listed on the affiliated organizations' website.

7.5 DISCUSSION

In this study of 28 Canadian guidelines produced or revised since the start of 2012, we found that FCOI relationships between guideline authors and drug companies are common. Authors disclosed FCOI with drug companies in twenty-one guidelines (75.0%). Relevant financial ties are also common amongst guideline authors, as authors in fifteen guidelines (54.0%) reported FCOI with manufacturers of drugs that they recommend as first-line treatments. Twenty authors on two or three guidelines disclosed

different FCOI in their statements. Eight guidelines identified affiliated organizations that had financial relationships with drug companies that manufactured drugs recommended for first-line treatment.

To our knowledge, our study is the first to systematically describe FCOI disclosures by authors on Canadian guidelines, as well as the financial relationships between the guideline-affiliated organizations and pharmaceutical companies. We used a population approach to guideline inclusion and did not exclude guidelines based on medical specialty or disease category.

This study contributes to existing international studies on FCOI disclosures across medical specialties, which have produced results similar to our findings. Cosgrove and colleagues (2009) found that in three psychiatry guidelines, 18 of 20 (90%) authors held FCOI with pharmaceutical companies and none of these ties were disclosed in the guideline. On two of the three guidelines assessed, 100% of the working group members possessed FCOI (Cosgrove et al., 2009). Neuman and colleagues (2011) found that in 14 guidelines on screening and/or treatment for hyperlipidaemia or diabetes published by national Canadian and American organizations between 2000 and 2010, 138 out of 288 (48.0%) panel members reported FCOI.

In a study analyzing 17 cardiovascular guidelines, Mendelson and colleagues (2011) found that 277 out of 498 (56.0%) authors reported FCOI. A 2013 study by Norris and colleagues (2013) found that in 13 guidelines for glycemic control in type 2 diabetes mellitus from the National Guideline Clearinghouse (NGC), the percentage of authors who disclosed one or more FCOI ranged from 0% to 94%. A 2013 Danish study found

that 135 out of 254 (53.1%) authors on 45 guidelines held FCOI and although FCOI were common, disclosures were rare (Brix Bindslev et al., 2013).

We believe that our results provide a conservative estimate of the prevalence of FCOI disclosed by guideline authors as we did not conduct external web or publication searches to determine the completeness of the FCOI disclosures in the guidelines. Our exclusion of 40 guidelines based on their lack of both FCOI disclosure sections and corresponding author contact information reflects findings that guidelines commonly contain no information about potential FCOI (Langer et al., 2012).

Finally, consistent with related research (Brix Bindslev et al., 2013; Weinfurt et al., 2008), 20 authors on two or three guidelines that we assessed disclosed different FCOI in their disclosures. These inconsistencies may be due to five factors: (i) journals in which these guidelines were published may have had different FCOI disclosure policies and requirements, (ii) endorsing professional medical societies and associations, as well as the medical journals in which CPGs are published, may have had differing policies on FCOI disclosure and permitted relationships, (iii) authors may have engaged in new FCOI relationships in the time between publishing guidelines, (iv) FCOI declarations may have been incomplete or missing completely, and (v) reliance on voluntary reporting of FCOI by authors may have resulted in underreporting of these relationships because of the subjective decisions of individual authors (Brix Bindslev et al., 2013; Papanikolaou et al., 2001; Taylor & Giles, 2005).

7.6 LIMITATIONS

We excluded guidelines if either authors or committee members were not explicitly named, limiting the scope of our analysis. Additionally, our analyses accounted for neither drugs that were recommended for second- or third-line treatment, nor the strength of evidence used to make first-line drug recommendations. We did not differentiate among the types of FCOI that the authors disclosed. Finally, we did not consider the funding source(s) of the guidelines. Our results are preliminary since our sample size of guidelines is limited.

7.7 CONCLUSION

Our findings support the need for future research to measure not only the prevalence, but also underreporting of FCOI in guidelines. Our results also suggest a need for accurate and consistent disclosures. Future research is also necessary to determine whether guideline authors' reported FCOI are associated with their drug treatment guideline recommendations.

After the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF) instituted new disclosure rules in 2010, the prevalence of guidelines with disclosures increased from 8% to 95% in 2011. This reform requires guideline-creating groups to ensure that both their members' declarations and the procedures used to declare, document, and the disclosures themselves are made public (Langer et al., 2012).

Physicians tend to have confidence in, and attribute value to, guidelines issued or distributed by official professional associations (Hayward, Guyatt, Moore, McGibbon, & Carter, 1997). Therefore, we encourage professional associations including the CMA to consider developing a policy equivalent to that which was adopted by the AWMF on FCOI disclosures and we recommend that the CMA refuse to list any CPGs that do not conform to these standards.

7.8 ACKNOWLEDGEMENTS

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FIGURE 7.1 GUIDELINE EXCLUSION CRITERIA AND PROCESS OF GUIDELINE EXCLUSION

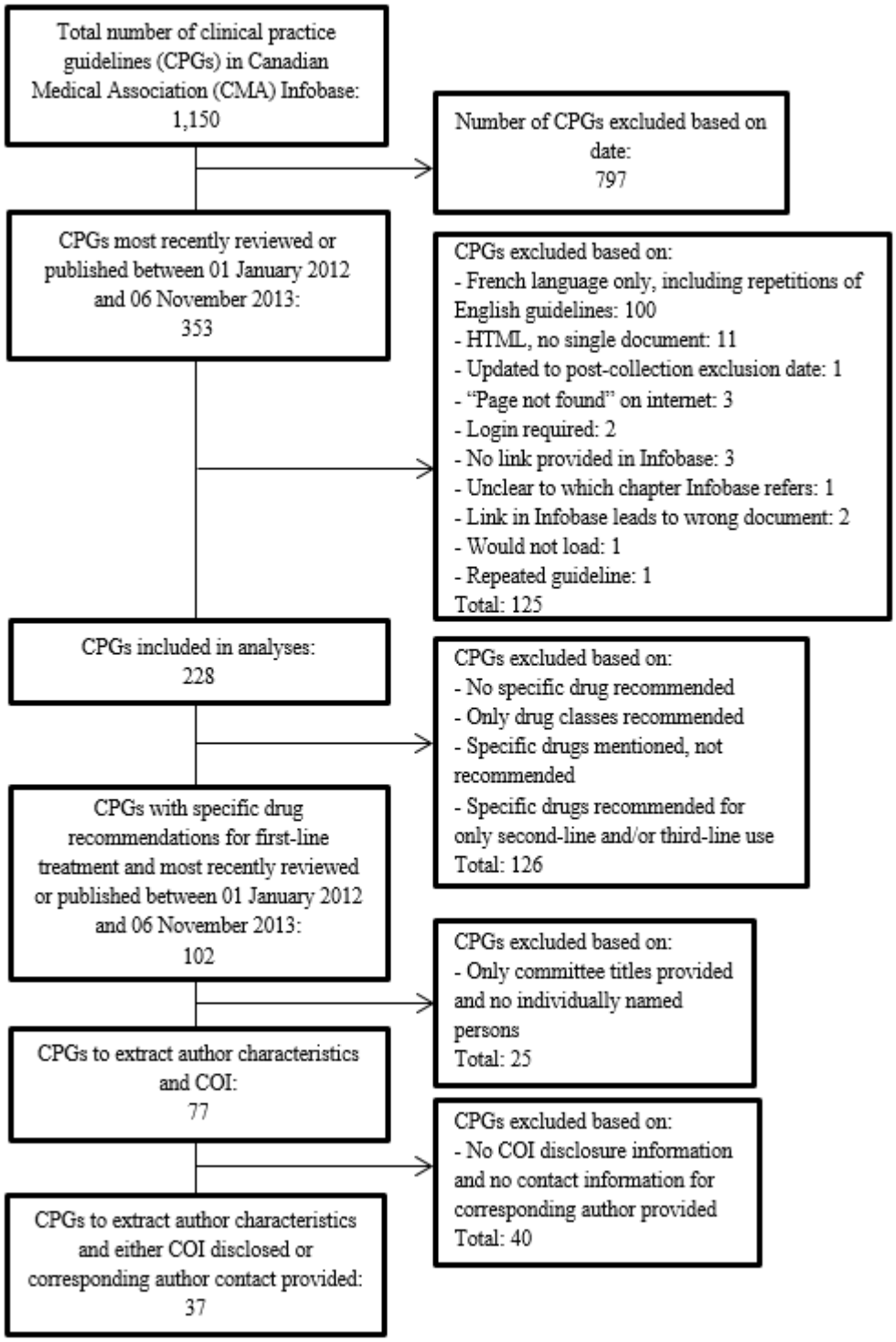

FIGURE 7.2 SUMMARY AND RESULTS OF LOCATING DISCLOSURE STATEMENTS

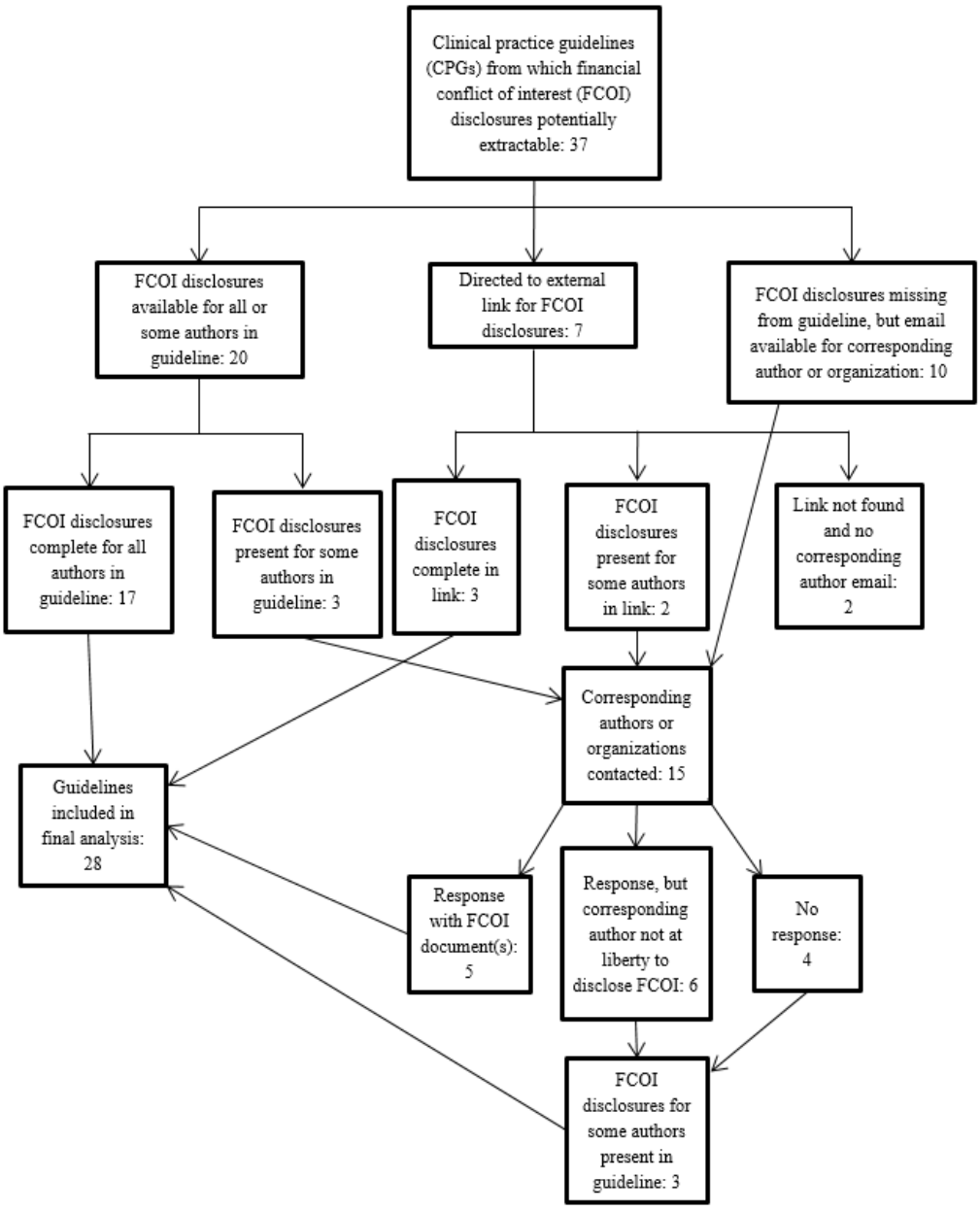

TABLE 7.1 SUMMARY OF FINANCIAL CONFLICT OF INTEREST (FCOI) DISCLOSURES BY GUIDELINE

Clinical practice guideline ID#	Year	On-patent drugs recommended (N)	Off-patent drugs recommended (N)	Disclosure statements assessed (N)	Assessed statements disclosing drug company FCOIs*, N (%)	Assessed statements disclosing relevant FCOIs, N (%)	Assessed statements disclosing non-relevant FCOIs, N (%)	Assessed statements disclosing vague FCOIs, N (%)	Assessed statements disclosing no FCOI or non-commercial conflicts, N (%)
5	2013	1	1	2	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)
7	2013	2	8	19	18 (95)	15 (79)	3 (16)	0 (0)	1 (5)
18	2013	0	4	22	0 (0)	0 (0)	0 (0)	0 (0)	22 (100)
27	2013	4	9	21	19 (90)	18 (86)	1 (5)	0 (0)	2 (10)
29	2013	5	7	25	18 (72)	6 (24)	12 (48)	0 (0)	7 (28)
35	2013	3	2	5	2 (40)	2 (40)	0 (0)	0 (0)	3 (60)
40	2013	3	3	13	0 (0)	0 (0)	0 (0)	0 (0)	13 (100)
44	2013	6	3	13	0 (0)	0 (0)	0 (0)	0 (0)	13 (100)
46	2013	7	0	9	9 (100)	4 (44)	0 (0)	5 (56)	0 (0)
93	2013	1	0	19	19 (100)	0 (0)	0 (0)	19 (100)	0 (0)
94	2013	3	15	22	15 (68)	10 (45)	5 (23)	0 (0)	7 (32)
103	2013	0	1	17	12 (71)	0 (0)	12 (35)	0 (0)	5 (29)
112	2012	2	0	4	4 (100)	3 (75)	1 (25)	0 (0)	0 (0)
242	2012	8	6	9	8 (89)	7 (78)	1 (11)	0 (0)	1 (11)
244	2012	0	1	19	8 (42)	0 (0)	8 (42)	0 (0)	11 (58)
258	2012	1	0	9	8 (89)	6 (67)	2 (22)	0 (0)	1 (11)
260	2012	1	2	3	3 (100)	3 (100)	0 (0)	0 (0)	0 (0)
267	2012	1	0	2	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)
269	2012	4	1	24	6 (25)	6 (25)	0 (0)	0 (0)	18 (75)
273	2012	1	1	23	2 (9)	2 (9)	0 (0)	0 (0)	21 (91)
274	2012	0	1	24	18 (75)	0 (0)	18 (75)	0 (0)	6 (25)
283	2012	2	0	13	0 (0)	0 (0)	0 (0)	0 (0)	13 (100)
289	2012	2	0	23	1 (4)	1 (4)	0 (0)	0 (0)	22 (96)
295	2012	3	1	25	1 (4)	0 (0)	1 (4)	0 (0)	24 (96)
299	2012	8	1	16	12 (75)	12 (75)	0 (0)	0 (0)	4 (25)
345	2012	2	1	8	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
349	2012	7	0	3	3 (100)	2 (67)	1 (33)	0 (0)	0 (0)
352	2012	1	2	8	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Totals				400	188	97	65	26	212

TABLE 7.2 UNIQUE AUTHORS' DECLARATIONS IN ONE, TWO, AND THREE GUIDELINES

Type of declaration	Number of unique authors making declarations in:		
	One guideline	Two guidelines	Three guidelines
FCOI* with drug companies	119	7	0
Non-commercial conflicts or no FCOI	162	21	0
Vague FCOI	21	0	0
FCOI with different drug companies	0	12	0
FCOI with drug companies in one or guideline, then vague FCOI in another guideline	0	1	0
FCOI with drug companies in one guideline, then non-commercial conflicts/no FCOI in another guideline	0	3	0
Non-commercial conflicts/no FCOI in one or two guidelines and vague FCOI in one or two guidelines	0	2	2
Total number of unique authors: 350			

*Financial conflicts of interest

CHAPTER 8

CONCLUSION

8.1 THE IMPORTANCE OF POLICIES ON FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS WITH THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry has had, and continues to have, the opportunity for pervasive involvement and engagement in financial conflict of interest (FCOI) relationships with physicians in the development and dissemination of medical education for undergraduate medical students and graduate practicing physicians. FCOI relationships between the pharmaceutical industry and physicians across medical specialties are common and can range from accepting incentives from drug companies, to accepting the role as speakers for companies, to participating as honorary authors of ghostwritten papers to be published in medical journals (Adair & Holmgren, 2005; Blumenthal, 2004; Campbell et al., 2007; Cosgrove, Krimsky, Vijayaraghavan, & Schneider, 2006; Fugh-Berman, 2010; McFadden, Calvario, & Graves, 2007; Morgan, Dana, Loewenstein, Zinberg, & Schulkin, 2006). Medical research is increasingly being conducted by, or in partnership with, the private sector (Downie & Herder, 2007; Lemmens & Luther, 2007). The potential risks of FCOI relationships in medicine are far-reaching and play out in the research, presentation, and dissemination of medical research.

FCOI relationships have been useful to the pharmaceutical industry for the purpose of knowledge creation and dissemination through various modes of medical education. The voluntary self-regulation model by which medical schools, medical journals, and professional medical associations are governed has allowed these institutions to develop, adopt and enforce policies on interactions with industry without outside scrutiny. In general, these policies have permitted both institutional and individual FCOI relationships, putting the primary objective of providing the best available balanced medical education at risk because of potential financial interests. The positioning of these interests by medical institutions can be observed in their policies through analyses, such as those carried out in the four studies within this dissertation. What policies say, and, importantly, what they fail to say, are indications of medical institutions' values and interests within the current scientific culture in which medical education and research is conducted and provided to medical students and practicing physicians. Neoliberal science has reoriented the medical research and writing processes to include such corporate practices as mass-scale hiring of contract research organizations (CROs), medical education communication companies (MECCs), and medical writing organizations (MWOs), ghostwriting and guest authorship, and the suppression of unfavourable data. The normalization of FCOI relationships is perpetuated as individuals with financial relationships with pharmaceutical companies continue to teach and publish medical educational materials. This teaching and publishing can occur within academic research institutions that also have financial partnerships with drug companies. The normalization of these practices has served to encourage shifts in the medical research culture, which

has spurred the development of social, financial, and professional parameters within which FCOI policies must operate.

Despite claims that seek to destigmatize FCOI relationships with industry and delegitimize and minimize arguments and efforts in favour of regulating these relationships (Barton, Stossel, & Stell, 2014; Rosenbaum, 2015a, 2015b, 2015c; Stossel, 2008a, 2008b), there is a substantive literature base that provides evidence to the contrary (see Chapter 2). The literature has found that, across various types of FCOI relationships through which drug companies promote their products, physicians can be unduly influenced. The FCOI relationships, in which drug companies and physicians participate, function as a vector by which companies can engage in both subtle and overt drug promotion. Drug companies recognize that, in the supply-demand equation, they provide the supply of products, while prescribing physicians are on the demand side (Gagnon, 2009).

In order to ensure that companies' supply is in demand, they must convince physicians that their products are the best for their patients and, as Marc-André Gagnon states, "[p]romotion is the missing link that unites all elements of breadth and depth into a workable and durable regime of accumulation for Big Pharma" (Gagnon, 2009). Rationally, companies would not continue to spend tens of billions of dollars annually (United States estimate, see Gagnon & Lexchin, 2008) on efforts that might not produce returns that outweigh their expenditures. These promotional efforts can take many forms within medical education in medical schools (Austad, Avorn, & Kesselheim, 2011; Busing, 2008; Downie & Herder, 2007; Ehringhaus et al., 2008; Epstein, Busch, Busch, Asch, & Barry, 2013; Hébert, MacDonald, Flegel, & Stanbrook, 2010; King, Essick,

Bearman, Cole, & Ross, 2013; Persaud, 2013; Zinner, Bolcic-Jankovic, Clarridge, Blumenthal, & Campbell, 2009), medical journals (Angell, 2008; Fugh-Berman, 2010; Kesselheim, 2011; Lundh, Barbateskovic, Hrobjartsson, & Gotzsche, 2010; Lundh, Sismondo, Lexchin, Busuioc, & Bero, 2012; McHenry & Jureidini, 2008; Melander, Ahlqvist-Rastad, Meijer, & Beermann, 2003; Smith, Gotzsche, & Groves, 2014; Smith, 2003, 2005), continuing medical education (CME) programs accredited by professional medical associations (Fugh-Berman & Hogenmiller, 2015; Lexchin & Vitry, 2012; Relman, 2001, 2003; Rothman et al., 2009; Schofferman et al., 2013; Spithoff, 2014; Steinbrook, 2008), and clinical practice guidelines (Abramson & Starfield, 2005; Brix Bindslev, Schroll, Gotzsche, & Lundh, 2013; George, Vesely, & Woolf, 2014; Institute of Medicine [IOM], 2011; Kung, Miller, & Mackowiak, 2012; Neuman, Korenstein, Ross, & Keyhani, 2011). Therefore, since there is limited literature that evaluates FCOI policies in Canada, it is important to conduct policy analyses on those which have been adopted by Canadian medical schools, medical journals that reach Canadian doctors, and Canadian professional medical associations. It is equally as important to conduct analyses on FCOI relationship disclosure practices by authors of Canadian clinical practice guidelines because these guidelines play a pivotal role in the way that doctors prescribe medications.

8.2 SUMMARY OF FINDINGS AND CONTRIBUTIONS TO THE LITERATURE

The four manuscripts that comprise the central chapters of this dissertation consider FCOI relationships between physicians and drug companies to be vitally important to the shaping, production, and dissemination of medical research in ways that

are conducive to industry's interests. Together, the four manuscripts illustrate the windows of opportunity for drug company interests to be expressed throughout medical education. This education extends broadly from undergraduate medical education, to peer-reviewed medical journals, to professional medical associations that host accredited CME programs for physicians, to clinical practice guidelines that physicians consult for treatment recommendations for their patients. The four manuscripts provide original studies in each of these areas. The research for two of these studies has resulted in two completely novel scoring tools for examining FCOI relationships.

8.2.1 "Too few, too weak: Conflict of interest policies at Canadian medical schools"

Students in Canadian medical schools are often taught by faculty who have FCOI relationships with drug companies (Hébert et al., 2010). These relationships have the potential to affect not only the academic and publishing interests of the faculty members, but also their professional medical opinions and the material that they teach to medical students (Cho, Shohara, Schissel, & Rennie, 2000; Downie & Herder, 2007; Ehringhaus et al., 2008; Zinner et al., 2009). Institutional FCOI relationships with the pharmaceutical industry, whereby drug companies provide resources for medical students within medical schools, can also affect the information that students receive and their attitudes toward industry information (Epstein et al., 2013; Ubelacker, 2010). To determine the extent to which medical schools in Canada permit or prohibit relationships with the pharmaceutical industry and protect their students from potential industry influence, we conducted a

systematic analysis of conflict of interest policies adopted by all 17 Canadian medical schools.

This study contributes a scoring tool that was modified from tools provided by supporting literature (American Medical Student Association [AMSA], 2012; Chimonas, Patterson, Raveis, & Rothman, 2011; Mason & Tattersall, 2011) to evaluate medical school policies on FCOI relationships with industry. In this study, the FCOI policies adopted by the Canadian medical schools were, in general, weak or permissive based on our scoring tool, indicating that policies adopted by medical schools generally did not discourage financial relationships with industry (Shnier, Lexchin, Mintzes, Jutel, & Holloway, 2013). Furthermore, over two-thirds of the medical schools in Canada had not, at the time of the study, required that the schools' medical students be taught about conflicts of interest and drug promotion in the curriculum. This gap in the education provided to medical students has important consequences for their abilities to not only understand the implications of FCOI relationships with industry, but also to be able to identify FCOI relationships, drug promotional activities, and to have the skill-set to evaluate the information with which they are faced both as medical students and practicing physicians once they graduate and begin treating patients. Future research in this area can update the results to include medical school policies on conflict of interest that have updated or adopted after 2013.

8.2.2 "Honest authorship: A glossary and assessment tool to help predict vulnerability to corporate bias in manuscripts submitted to medical journals"

Peer-reviewed medical journals are a central medium on which medical professionals rely at all stages of their careers to obtain important information and research on diseases and conditions, treatment and prescribing choices, and medical case studies. Research published in even the most highly regarded peer-review medical journals has been questioned because of the realization of the increasingly pervasive roles of drug companies and their hired CROs, MECCs, and MWOs in, in some cases, virtually all stages of the research and publishing processes (Fugh-Berman & Dodgson, 2008; Fugh-Berman, Pike McDonald, Bell, Bethards, & Scialli, 2011; Fugh-Berman, 2005, 2010; Goldacre, 2012; Gotzsche, 2013; Healy, Mangin, & Antonuccio, 2013; Healy, 2012; Le Noury et al., 2015; Lexchin, 2012; Matheson, 2008; Melander et al., 2003; Mirowski & Van Horne, 2005; Ninan, Poole, & Stiles, 2008; Rothman, Brudney, Adair, & Rothman, 2013; Sismondo & Doucet, 2010; Sismondo, 2011; Smith, 2003; Steinman, Bero, Chren, & Landefeld, 2006; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008).

This study provided an analysis of the corporate scientific and medical publishing cultures, which acquiesce to corporate values that are consistent with neoliberal science and the commodification of knowledge at the expense of publishing impartial information. As the gatekeepers to publishing research, medical journals and their editors possess decisive authority over policy adoption, enforcement, and the acceptance or rejection of manuscripts. Medical journals are, therefore, in a unique position to verify and ensure that their policies on FCOI relationships, disclosures, and the spirit of those policies are being adhered to. This study does not have an exclusively Canadian focus; however, the results

are still applicable to Canada because Canadian medical students, doctors, and patients often consult international medical journals for medical information.

The terminology and spirit of these policies is of express importance considering the current landscape of the corporate scientific publishing culture, which is comprised of practices, now considered normative, that ensure the business goals of the sponsor. These practices skew the medical literature base in favour of drug companies' business interests. Informed by works by Mirowski (2001, 2012) Mirowski and Van Horne (2005), and Sismondo (Sismondo & Doucet, 2010; Sismondo, 2004, 2007, 2011), this study provided a discourse analysis of not only the landscape of scientific research in the interest of the corporation, but also the accompanying terminology that has allowed corporations to have hidden, behind-the-scenes involvement in research and publishing at all stages of these processes. A literature review resulted in a glossary of 50 terms, which were accompanied by support from the literature, illustrating the importance of these terms in the context of medical publishing. The terms that comprise the glossary were then used to develop an accompanying original evidence-based assessment tool that can be used, or modified and then used, by researchers in future development of medical journal policies that are effective in detecting biased submissions. This could be completed through conducting a pilot study on the assessment tool by partnering with a medical journal to distribute the tool to prospective authors regarding their submitted manuscripts. Together, the researchers and journal editors could analyze the responses on the assessment tool in the context of the submitted manuscript to determine whether it possesses characteristics of corporate science that make it vulnerable to bias. This assessment tool can also be used to

assess the research and publishing practices that journals consider to be important enough to include within their policies.

As the shift to corporate science continues, the scientific literature is heavily influenced by commercial messaging in medical journals. Medical journals are one vector by which medical professionals receive medical information that should be trusted to provide balanced and accurate data and conclusions. Therefore, it is the responsibility of medical journals to ensure that they adopt and enforce policies that demand high standards for transparency pertaining to the research and publishing processes. Medical journals reach wide audiences of physicians, as do CME programs. CME programs that are hosted by PMAs reach all Canadian physicians and, so, their policies on FCOI are also important to evaluate.

8.2.3 "Continuing medical education and pharmaceutical industry involvement: An evaluation of policies adopted by 60 Canadian professional medical associations"

The current literature on commercial sponsorship of CME programs argues the need for policy analysis of the development, content, and presentation of CME within the Canadian context (Bernat, Goldstein, & Ringel, 1998; Brody, 2010; Kassirer, 2007; Relman, 2003; Rothman et al., 2009; Steinbrook, 2008). To address this need, this study provides a systematic analysis of conflict of interest and industry involvement policies adopted by 60 PMAs in Canada, including the College of Family Physicians of Canada (CFPC) and the Royal College of Physicians and Surgeons of Canada (RCPSC). These 60 associations are recognized in Canada, by their membership, as authoritative and trusted

providers of CME programs for Canadian doctors. For each of the 60 associations, we collected the policies that they had adopted concerning relationships with industry and FCOI relationships as they pertained to CME programs. Because the current literature had not provided any policy scoring tools, we created a scoring tool in order to evaluate the policies.

The scores that the medical associations received were generally weak. Twenty-six associations had either no policies or their policies did not address the items in the scoring tool. None of the policies received scores that represented a restrictive policy for any item in the scoring tool. The highest average scores were received in the areas of commercial involvement in planning CME activities, presence of a review process for CME activity topics, and content review for balanced information. The lowest scores were received in the areas of awards, industry personnel, representatives and employees, distribution of industry-funded educational materials at CME activities, and distinction between marketing and educational materials.

This study contributes an original scoring tool to the literature. This tool is based on supporting literature (Barnes et al., 2007; Dyck & Kvern, 2008; Kassirer, 2007; Rothman et al., 2009; Takhar et al., 2007) that speaks specifically to CME programs. The scoring tool is supported by the literature on industry involvement in CME and helps to determine not only the extent to which industry involvement in CME programs is permitted, but also the degree to which medical associations retain control over the planning process and content of CME programs. Future research in this area can update the results to include Canadian medical associations' policies on industry involvement in CME that were adopted after completion of this study. For example, the RCPSC adopted

a new policy in 2016 (Royal College of Physicians and Surgeons of Canada [RCPSC], n.d.) that will be enforced beginning in 2018 (McLean & Bruser, 2016), so if an update of this study were to be conducted after 2018, this policy would be included in the analysis.

8.2.4 "Reporting of financial conflicts of interest in clinical practice guidelines: A case study analysis of guidelines from the Canadian Medical Association Infobase"

Clinical practice guidelines (CPGs) play a pivotal role in not only informing physicians about treatment standards, but also in decision making in physicians' prescribing and treatment choices for their patients. CPGs are widely distributed by professional medical associations and consulted by physicians for the best available clinical evidence; however, the development of CPGs has attracted debate. Despite recommendations that guideline development should be transparent, rigorous, and use scientific evidence, clinical experiential knowledge, and patient values to inform and improve recommendations (IOM, 2011), international studies have called into question whether guidelines are developed in this manner. These studies have found that many guidelines have made recommendations based on expert opinion rather than clinical trial data, consensus statements and retrospective case studies rather than data that has integrity and are based on incomplete and inappropriate use of available evidence (Abramson & Starfield, 2005; Cosgrove, Bursztajn, Krimsky, Anaya, & Walker, 2009; Dinnes, Hewison, Altman, & Deeks, 2012; Kung et al., 2012; Mendelson, Meltzer, Campbell, Caplan, & Kirkpatrick, 2011). Furthermore, concerns about the validity of guideline

recommendations have been raised because of the potential for bias during the guideline development process (Bell et al., 2013; Guyatt et al., 2010; Spielmans & Parry, 2010).

Studies on guidelines in the United States and Europe have demonstrated concern regarding the prevalence, underreporting, and consistency of guideline authors' disclosures of their FCOI relationships with the pharmaceutical industry (Brix Bindslev et al., 2013; Choudhry, Stelfox, & Detsky, 2002; Cosgrove et al., 2009; Langer et al., 2012; Mendelson et al., 2011; Neuman et al., 2011; Norris, Holmer, Ogden, Burda, & Fu, 2013; Papanikolaou et al., 2001). To provide an assessment of authors' FCOI relationship disclosures on clinical practice guidelines in Canada, we conducted a case study analysis on authors' disclosure statements in 28 guidelines, most recently reviewed or published in 2012 or 2013, drawn from the Canadian Medical Association Infobase. It is reasonable to analyze guidelines reviewed or published during this time because the issue of FCOI disclosures of guideline authors was, and continues to be, a relevant and public issue. We found that, in general, guideline authors commonly disclosed FCOI relationships with industry.

FCOI relationships held by the authors were often with the drug companies that manufactured the medications recommended as first-line treatments in the respective guidelines. We also found that some authors who were on more than one guideline disclosed different FCOI relationships in their statements across guidelines. The findings from this study support the need for additional research to assess the prevalence of FCOI in guidelines in relation to recommended drugs in guidelines. For example, future research which assesses the quality of evidence used in guidelines where the authors have FCOI relationships and whether the recommendations reflect the evidence would be valuable.

Future research in this area can update the results to include guidelines that have been most recently reviewed or published in 2014 and 2015.

8.3 INTERPRETING THE RESULTS

The four Mertonian norms of science (i.e., universalism, communism, disinterestedness, and organized skepticism) (Merton, 1942) work together to create a culture of science in the public interest, openness, and critical analysis. If the Mertonian norms of science are considered to be the embodiment of the scientific ideal, then the analyses within this dissertation show that they have all been violated. Disclosure has been used by medical educational institutions as a mechanism for allowing both individual and institutional FCOI relationships to exist, without addressing the effects of the presence of these relationships. To fully appreciate the results found within the manuscripts of this dissertation, they must be considered within the broader FCOI literature discussed in the literature review. The addressing of FCOI relationships in policies as needing to be disclosed, but not avoided, indicates not only that these relationships have come to be considered as normative, but also complacency within large institutions to realize the importance of the effects of corporate bias to the foundation of medical knowledge.

Transparency regarding the outsourcing of clinical research to CROs, funding of research, as well as origination of, ownership of, and access to data are significant to consider in the context of individual and institutional FCOI relationships with the pharmaceutical industry. Employing the Mertonian norms of science help to understand how far corporate scientific behaviours have deviated from the assumed scientific research

and knowledge dissemination roles. Objective science and scientific claims that can be evaluated based on their content and not on the characteristics of the scientists that make the claims (universalism), cannot be achieved without access to the content, or data, within the public commons (communism). Objective and scientific claims cannot be verified as being free of appropriation for interested purposes, such as its commercialization for sale to the public using mysticisms (i.e., promotional messages) expressed in scientific terms via education (disinterestedness), without access to data (again, universalism) and the opportunity to freely and critically analyze and scrutinize the data as fact and through competing perspectives (organized skepticism). The maintenance of the culture of FCOI relationships with the pharmaceutical industry and industry involvement as the norm, sometimes at all levels of medical research, writing, and education, indicates the broad unwillingness to comply with Mertonian norms of science in the public interest. Rather, in conformity with characteristics of neoliberal corporate science, the extensive and pervasive involvement of industry in medical education, generally, serves to ensure that data sharing, transparency, an understanding of corporate roles within medical research and publishing, and critical analyses of both data and these roles are never fully realized by those outside of the industry.

The generally permissive institutional policy responses to not only FCOI relationships with the pharmaceutical industry, but also industry involvement in all levels of medical research, writing, and education has significant implications for science in the public interest. The general lack of strong policies limiting and eliminating FCOI relationships with drug companies and industry involvement in medical education indicates the continuation of the shift towards neoliberalism and particularly neoliberal

science and marketplace of ideas. The broad willingness of medical educational institutions to adhere to neoliberal ideology may seem unnoticeable or trivial at the individual-level and in the day-to-day operations of these institutions; however, systematic structural analysis indicates that this adherence, even if unintentional, is profound. In practice, weak policies that do not effectively address FCOI relationships, industry involvement in medical education, and the potential for corporate bias present a façade of regulation. Rather than effectively regulate, the permissive policies create a façade that provides a false sense of oversight of FCOI relationships with the pharmaceutical industry. In this way, permissive policies have an effect that is opposite to that which may have been intended upon policy adoption. While the intended outcome may have been to limit FCOI relationships and the potential for bias in medical education, the outcome of permissive policies is that they pave the way for relationships with industry that individuals interpret as being acceptable according to these policies.

In accordance with neoliberal corporate bias theory, the minimalist role of medical institutions in the regulation of industry involvement of medical education may be represented by the largely weak or non-existent policies adopted in this area by medical educational institutions. Neoliberal corporate bias theory, in the context of medical institutions, has allowed for the critical analysis of the interests of these institutions, as represented by their policies. Although medical educational institutions may possess their own interests of providing medical education to physicians, medical students, and medical researchers, as well as cost-containment strategies, the general allowance of industry funding and involvement indicates a cooperative relationship between these institutions and the industry. This cooperation, or pro-business deregulation, has resulted in policies

that are biased in favour of partnerships or accommodating financial ties with industry, rather than the commitment to the pursuit of unbiased medical educational information for dissemination. Consistent with neoliberalism, the policies analyzed within this dissertation generally take a minimalist role in regulation, while still allowing FCOI relationships and institutional financial partnerships with industry to exist. The potential for neoliberal corporate bias is expressed through the orientation and interests of the policies, which, by virtue of their permissiveness, implicitly express the value of both individual and institutional FCOI relationships with the pharmaceutical industry.

The adherence of medical institutions to neoliberal ideology has been paralleled by the broad normalization of pro-industry behaviours that are amenable to the commercialization and privatization of medical knowledge. These pro-business behaviours have taken precedence over public health. For instance, in each of the four manuscripts, FCOI relationships with industry are in some way "managed" rather than avoided. The manuscripts that evaluated conflict of interest policies at Canadian medical schools (chapter 4), Canadian medical associations (chapter 6), and conflict of interest disclosures in clinical practice guidelines (chapter 7) found that FCOI relationships with drug companies were managed through disclosure. Disclosure is a mechanism by which the effects of FCOI relationships on medical education are perceived to be mitigated; however, the act of disclosure does not liberate data or its interpretations from secondary financial interests. The shortcomings of disclosure as a management solution for the presence of financial relationships with industry will be discussed in the next section. The manuscript that analyzed the neoliberal corporatized culture of medical research and publishing in medical journals (chapter 5) argued that the roles of "authors" and the drug

promotion industry in medical research and publishing have been transformed to acquiesce to the control over manuscripts that drug companies have required. The coding of the roles held by research and writing organizations to be muted so as to mask the true involvement of industry in the medical research and writing processes led to the development of a glossary of these terms and an accompanying assessment tool that aims to help predict the vulnerability of a particular manuscript to corporate bias. This tool attempts to provide a method by which roles in the medical research and publishing processes can be made to be transparent to take steps toward modestly achieving the Mertonian norms of science.

8.4 MANAGING FINANCIAL CONFLICT OF INTEREST RELATIONSHIPS: IS DISCLOSURE THE SOLUTION?

Each of the studies within this dissertation advocated for strengthening policies on relationships between physicians and the pharmaceutical industry to eliminate FCOI relationships that can reasonably be considered to increase the risk of industry influence in medical practice. A common characteristic across the two scoring tools and assessment tool produced within these studies is that each tool advocates for disclosure of FCOI relationships with industry when policies do not prohibit these relationships altogether. Comprehensive disclosure of FCOI relationships is considered to be the most basic requirement for the transparent reporting of FCOI relationships and to allow for informed decision-making and understanding by the audience (Lemmens & Luther, 2007). Where

FCOI relationships cannot be eliminated, disclosure of these relationships is important – as a first step.

Disclosure of FCOI relationships is often considered to be an acceptable solution and has been accompanied by the rationale that disclosing these relationships provides medical professionals and the public with reassurance that the information that is being published or presented has been guided by public health, rather than commercial interests (Lexchin & O'Donovan, 2010). This rationale assumes that relationships with industry are inevitable and that disclosure effectively addresses the problem of potential bias in research and the presentation of information (Kesselheim et al., 2012). However, disclosure on its own cannot be the solution to the potential influence of industry on research and publishing practices through FCOI relationships.

Although disclosure is a good first step to being able to evaluate the context in which the information was developed and disseminated, the effectiveness of disclosure as the solution to the influence resulting from FCOI relationships is limited by a number of factors. The nature of disclosure is such that it requires an audience to subjectively interpret and understand the disclosures. Subjective interpretation and understanding places the onus on the individual medical student, physician, or patient to determine the meaning, context, and potential risk of bias associated with the FCOI relationship(s) being disclosed. For instance, Kesselheim and colleagues (2012) found a clear relationship between funding disclosure variations and physicians' perceptions of a trial's rigor and results. In this study, regardless of the trial's actual study design, if pharmaceutical industry funding was disclosed in the study, physicians were less likely to perceive the

trial as having a high level of rigor as compared with studies in which a disclosure statement was absent (Kesselheim et al., 2012).

Jeffrey Drazen, current editor-in-chief of the *New England Journal of Medicine*, published a criticism of Kesselheim and colleagues' article, stating that physicians' skepticism of industry funded research is a disproportionate response to a select few cases of drug company misrepresentation of data in the media (Drazen, 2012). Drazen (2012) declares that "[w]e at the [*New England Journal of Medicine*] think that decisions about how trials influence practice should be based on the quality of information conveyed in the full study report" (p. 1152) and continues that the *Journal* adheres to trial registration requirements in ClinicalTrials.gov and FCOI disclosure requirements as set out by the International Committee of Medical Journal Editors (ICMJE). Drazen (2012) argues that because the *New England Journal of Medicine* has taken these steps, we should "believe the data". He argues that, trial participants, in their altruism in their contributions to science ought to be respected without concern for the source of study funding. He argues that interpretations of study validity should be based on study design, the quality of data collection, and the fairness of results reporting (Drazen, 2012). In an environment in which clinical research is conducted according to Mertonian norms, Drazen's plea to "believe the data" might be more convincing; however, the public, physicians, and academics cannot be justifiably expected to simply trust that sound methodologies, as they are reported in published clinical trials, indicate unbiased collection, analysis, reporting, and interpretation of results. Lundh and colleagues' (2012) found that industry funded trials are just as methodologically rigorous as non-industry funded trials; however, regardless of the methodological rigor of industry-funded studies, bias can still appear within the

research question or elements of the design of trials that are not measured by the tools that are commonly used. Furthermore, regardless of methodological rigor, published studies sponsored by industry tend to report favourable efficacy results and conclusions more often than non-industry sponsored studies (Flacco et al., 2015; Lexchin, Bero, Djulbegovic, & Clark, 2003; Lexchin, 2012; Lundh et al., 2012).

Furthermore, clinical trial registration is not, by itself, an indicator of reliable results. Since clinical trial registration within a year of study completion was required by United States legislation in 2008, the legislation has been ignored by 60 percent to 90 percent of trials (Anderson et al., 2015; Goldacre, 2013). Furthermore, clinical trial registration does not necessarily mean that the results of these trials are reported or published in a timely manner, or at all. In fact, Iain Chalmers, Paul Glasziou and Fiona Godlee (2013) argue that the systemic underreporting of clinical trial data has continued, despite the requirement to register trials. Chalmers and colleagues (2013) estimate that only approximately half of all registered trials publish at least some of their results.

Clinical trial results that are published may be accompanied by FCOI relationship disclosures. Once the onus is placed on the audience, e.g., medical students or medical professionals, to interpret FCOI disclosures, it is their responsibility to also interpret the information that precedes or follows the disclosures. The audience may assume that once, or because, an author or speaker made an FCOI disclosure that all information following the disclosure is unbiased, uninfluenced, and accurate. Disclosure may also lead an individual to the conclusion that the presenter or author has been involved in all steps of the research and writing of the study that they are presenting. This assumption cannot be made, especially within the corporate medical research culture in which CROs, MECCs,

and MWOs play a role in the research and writing processes of studies and presentations (Rothman et al., 2013; Sismondo, 2011).

Disclosure may also unintentionally lead physicians to provide biased recommendations because of two mechanisms that Loewenstein and colleagues (2012) explain: strategic exaggeration and moral licensing. Strategic exaggeration, the authors explain, is the tendency for the person who is disclosing FCOI relationships to provide more biased advice that is meant to counteract any anticipated discounting of their recommendations as a result of their disclosures. The concept of moral licensing explains an unconscious feeling whereby authors or presenters may feel that providing biased advice is justifiable because the audience has been cautioned by their disclosure (Loewenstein, 2012). The notion that "consumers know best" informs the widespread adoption of disclosure and provides the recipients of the disclosures with a false sense of empowerment and pseudo-accountability that allows FCOI relationships and disclosures to continue on as the norm (Wilson, 2014). Furthermore, an audience that has not undergone the necessary education about the risks of influence and bias associated with both individual and institutional FCOI relationships may interpret FCOI disclosures as a prestigious list of affiliations and achievements that they should also seek throughout their medical careers.

Disclosure does not prevent future scandals (Wilson, 2014), but, as a management strategy, it can eliminate the need for strong policy reforms or conflict of interest regulation of any kind (Cain, Loewenstein, & Moore, 2005). Disclosure also relieves those who are making the disclosures from their responsibility for adverse outcomes from their recommendations. Disclosure does not mitigate the potential consequences that may result

from FCOI relationships between physicians and industry, but, instead, serves as a type of warning or indication mechanism that signals to the audience that the burden of interpreting any results has been shifted to the audience.

8.5 DISSERTATION LIMITATIONS

The studies that are included in this dissertation have some common limitations. First, we did not conduct interviews to accompany our policy analyses. Interviews may have provided valuable insights into both the interpretation and enforcement of the policies. Second, we did not evaluate educational programs that fell under the purview of the policies that we analyzed; therefore, we were not able to determine whether, or how, any potential bias may have manifested in these educational programs. Finally, we have not analyzed whether perceived weaknesses in policies actually result in harm to patients.

8.6 FINAL STATEMENT AND FUTURE DIRECTIONS

The four manuscripts are complementary to each other because they each provide an analysis of important and far-reaching types of medical education in the context of increasingly corporatized science. Each study consistently found opportunities in policies, as guiding and standard-setting documents, for pharmaceutical industry promotional influence in every interstice of the medical profession. FCOI relationships with the pharmaceutical industry occur on a continuum ranging from the individual to institutional

levels of medical research. Sismondo (2011) has stated that "…the value of academic disguises outweighs the cost of…scandals." These academic disguises have been revealed as early as medical school, through to CME programs hosted by PMAs, published papers in medical journals, and clinical practice guidelines. This pervasive presence of the pharmaceutical industry in medical research at each of these levels has aligned the goals of research endeavours to be conducted in the interest of neoliberal science.

Industry involvement in medical education manifests in ways that are not immediately, or at all, clear to the intended audience. One must not only understand the language of corporate science, but also possess the ability to decode this language to comprehend the behind-the-scenes roles and influence of pharmaceutical, and supporting, companies in the production of "science". For instance, the academic concept of publication planning, describing the behind-the-scenes role of a drug company in strategically developing and positioning its products favourably in the medical literature, is not a widely known phenomenon outside of industry and the research area on industry involvement in medical research. Likewise, a medical student, physician, or member of the public who is reading a peer-reviewed journal article with the acknowledgement of "editorial assistance" or a "medical writer" might not realize that this language, de-coded, may disguise the deep involvement of the drug promotion industry in a strategic endeavour to represent a drug favourably.

There remains room for important improvements to be made to the policies that have been adopted by Canadian medical schools, Canadian professional medical associations, and medical journals that reach Canadian doctors to protect the interests of physicians, medical students, and the Canadian patient population. In addition, the

integrity of medical education at all stages and the resultant recommendations made by physicians to the Canadian patient population about treatment must also be protected from undue industry influence. In a medical culture in which FCOI relationships are common, unbiased and balanced medical research and publishing ought to be protected by policies adopted by the medical institutions that are considered to be the most authoritative in medical education.

Conflict of interest policies adopted by authoritative medical institutions that provide medical education can be strengthened by inviting the engagement of medical students, physicians, medical and health policy researchers, medical schools, medical research institutions, professional medical associations, and public and private health insurers (IOM, 2009). This engagement may encourage the adoption, implementation, and enforcement of conflict of interest policies while, simultaneously, defining and endorsing a culture of accountability that values and provides the professional standards necessary for achieving transparency in medical research and publishing processes (IOM, 2009). Should authoritative medical research and education institutions and associations not voluntarily strengthen their policies on FCOI relationships with drug companies, it is likely that pressure will increase for regulatory reform from sources external to these institutions (IOM, 2009).

Rather than remediation of bias or mistrust after participation in FCOI relationships, any policy reform should be informed by the precautionary principle and be aimed primarily toward protecting the integrity of medical professionals' judgement and ensuring that public confidence and trust in medicine is preserved (IOM, 2009; Lemmens & Luther, 2007; Lexchin & O'Donovan, 2010). For example, if it is widely understood

that FCOI relationships with the pharmaceutical industry and industry involvement in medical research and education have the potential to expose content to corporate biases, the precautionary principle would argue that these relationships should be avoided. By way of contrast, the risk management perspective would argue that these relationships need not be prevented, but managed through disclosure, for example. Importantly, these goals can be realized only with policies in place that are clearly described and interpreted and accompanied by very clear and enforceable sanctions that are publicly accessible. The standard should be for medical professionals to avoid FCOI relationships and undergo training, as part of their undergraduate education or accredited CME programs, on FCOI relationships with industry – how to identify them, alternatives to engaging in them, and how to mitigate their risks.

The current approach, which is generally permissive, that allows relationships with industry in medical education, will likely remain in place in the foreseeable future. Therefore, until the perspective that non-conflicted medical professionals ought to retain control over the research and publishing processes gains traction, disclosure and transparency, together, will be the prime approach to the contextual understanding and interpretation of published articles and presentations for physicians, medical students, and the public.

Small-scale initiatives for effective conflict of interest disclosure and transparency could be achieved at the institution level by developing databases that contain FCOI relationship disclosures, for example, within universities, hospitals, and professional medical associations. These databases could be cross-referenced with each other. A large-scale method by which financial conflict of interest disclosures within the medical

profession may become more transparent is through the creation of a unified publicly accessible online database that aggregates conflict of interest disclosures.

Online FCOI relationship disclosure efforts of this type already exist. For example, the United States Physician Payment Sunshine Act (PPSA) database is housed and managed online by the Centers for Medicare and Medicaid Services (CMS.gov, 2016). Rochon and colleagues (2010) provide a FCOI relationship checklist that covers administrative, study, personal financial, and authorship stages of the clinical research process. A disclosure checklist, such as the one that Rochon and colleagues (2010) recommend, could be systematically collected and housed in an online publicly searchable database. Another example of a disclosure effort is the free downloadable Google Chrome browser application ("app") that was created at the Hacking iCorruption hackathon event co-sponsored by the Edmond J. Safra Center for Ethics at Harvard University and the MIT Center for Civic Media (Baugh, 2015). The app, called "Unearth" extracts funding and conflict of interest information from PubMed research articles that users view and puts this information on the abstract page of PubMed articles. This innovative approach counters the problem that sometimes disclosures are not available in manuscripts or on websites external to publications. This up-front viewing of disclosures, rather than viewing the disclosures after reading the article or not at all, allows readers to first pay attention to FCOI relationships prior to reading the article (Baugh, 2015). Readers' interpretations of FCOI relationships in these cases remains an issue, but with the help of intermediaries such as consumer watchdog groups in Canada (e.g., Transparency International, which has a Canadian branch (Transparency International, 2015),

Retraction Watch (2016), and Democracy Watch (Democracy Watch, n.d.), understandings of disclosures could become clearer (Loewenstein, 2012).

Although disclosures have limitations on an individual practical-use basis, analyses of disclosures can be very helpful in discourse analyses of medical education and the proverbial strings that may be attached to educational information. For this reason, a comparative analysis of the findings in our Canadian medical schools study (Chapter 4) and any reformed or newly adopted policies would provide insights into the changing values and interests of these institutions. The glossary and policy scoring tool developed in Chapter 5 may also be practically applied to the analyses and development of medical journals' conflict of interest policies. Our analysis of policies adopted by Canadian PMAs on industry interaction in CME programs (Chapter 6) would be complemented by an analysis of potential biases in the CME programs held by these associations. Finally, our analysis of conflict of interest disclosures made by authors on clinical practice guidelines (Chapter 7) would contribute to analyses of the journal policies in which these guidelines are published, as well as the guideline development policies adopted by Canadian PMAs.

The forward momentum for the adoption and enforcement of policies concerning FCOI relationships has been subject to a serious attack from those who argue that FCOI relationships are not a source of influence (Barton et al., 2014; Rosenbaum, 2015a, 2015b, 2015c; Stossel, 2008b, 2015). These views against adopting strong policies on FCOI relationships have in turn received pushback from high-profile sources (Angell, 2008, 2009; Kassirer, 2005, 2007; Lexchin & O'Donovan, 2010; Lexchin & Vitry, 2012; Prasad, 2015). Research on FCOI relationships and policy development is still a deeply contested

terrain; therefore, the reforms suggested in this dissertation are by no means foregone conclusions.

The manuscripts within this dissertation contribute to the conflict of interest literature a starting point for research into FCOI relationships in the various Canadian medical education contexts. Mirowski and Van Horne (2005) have argued that medical education and scientific research become successfully privatized when the boundary between scientific research and marketing is blurred to the point at which they are indistinguishable from each other and the difference between promotional messages and scientific research results is impossible to identify. It could be argued that weak policies on both pharmaceutical industry relationships in medicine and industry involvement in medical education are contributing to the successful privatization of medical education and scientific research in the Canadian context. Therefore, it is important to continue to conduct critical and evaluative analyses of conflict of interest and industry involvement policies that have been adopted by the various institutions that provide medical education.

Based on the works within this dissertation, future research directions include policy evaluation updates and further analyses of the medical education context in terms of opportunities for industry involvement in order to keep up-to-date on not only the policies, but also the practices of scientific research and management and medical education within the culture of neoliberal science. First, an update to the analysis of Canadian medical schools' conflict of interest policies (Chapter 4) would potentially provide analyses of new and updated policies by the medical schools since the study was published in 2013. An updated analysis would also determine how or whether the new policies provide more, less, or the same level of restrictive standards for both institutional

and individual relationships with the pharmaceutical industry in medical schools. Additionally, an important study in this context could assess whether these policies have a role in the day-to-day activities of the schools and their faculty and students. Furthermore, perhaps an initiative like the American Medical Student Association (AMSA) Scorecard online could help to encourage continued policy development in this area (AMSA, 2012).

Another important update to the policy evaluations within this dissertation is on the continuing medical education policies adopted by the professional medical associations in Canada. For example, the College of Family Physicians of Canada has developed a new standard that is set to come into effect in 2018. This standard pertains to external influence that could lead to bias in its CME (McLean & Bruser, 2016; The College of Family Physicians of Canada [CFPC] & Royal College of Physicians and Surgeons of Canada [RCPSC], n.d.). This and other potentially new or updated documents are important to analyze and evaluate in the context of previously adopted policies to determine whether they add strength to policies or maintain the status quo. Another important study could analyze how or whether the restrictiveness of policies affects the content of continuing medical education hosted by Canadian professional medical associations.

The medical journal glossary and assessment tool should be considered as living documents to be used together and updated as new terms or new interpretations are realized. The assessment tool should be pilot tested and revised, if necessary, for future use to help to assess the potential for bias in manuscripts submitted to medical journals. Future studies in each of these areas should continue to consider both institutional and

individual FCOI relationships as structural phenomena, the standards for which can be set and regulated fairly and equally across areas of medical education. FCOI relationships must also be considered in terms of patient health, as previous research has documented patient harms that have resulted from science management under neoliberal science (Le Noury et al., 2015; Elliott, 2010, 2011, 2012, 2014).

In order for medical students, physicians, and the public to receive truly independent scientific information about the safety and effectiveness of pharmaceutical products and to protect the interests of patients, medical research will have to be conducted by non-conflicted, independent agencies and similarly disseminated by non-conflicted, independent professionals (Goozner, 2004). Although difficult, many of the present FCOI relationships can be controlled, reduced, or rendered harmless through health policy reform (Rodwin, 1993). Responsibility for not only policy reform, but also setting professional standards for interactions with industry, rests, first, with the very medical institutions that are so widely considered to be authoritative in the provision of medical education: medical schools, professional medical associations, and medical journals.

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CO-AUTHOR AGREEMENT FORMS

STATEMENT OF AUTHORSHIP

CO-AUTHORSHIP AGREEMENT: INCLUSION OF MANUSCRIPT IN DISSERTATION

Title of Study: Too Few, Too Weak: Conflict of Interest Policies at Canadian Medical Schools

Author 1: Adrienne Shnier

Performed the study, interpreted and analyzed the data, wrote the manuscript, and finalized the manuscript.

I certify that this statement of contribution to the above named paper is correct and give my consent to Adrienne Shnier to include our co-authored manuscript in her doctoral dissertation in partial fulfillment of the degree of Doctor of Philosophy in the Graduate Program of Health at York University.

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Author 2: Joel Lexchin

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Performed the study, interpreted and analyzed the data, wrote the manuscript, and finalized the manuscript.

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Author 4: Anne-Marie Jutel

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Author 5: Kelly Holloway

Performed the study, interpreted and analyzed the data, wrote the manuscript, and finalized the manuscript.

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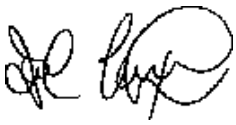
Signed:  Date: July 23, 2015

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Author 5: Kelly Holloway

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Kelly Holloway

STATEMENT OF AUTHORSHIP

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Title of Study: Reporting of Financial Conflicts of Interest in Clinical Practice Guidelines: A Case Study Analysis of Guidelines from the Canadian Medical Association Infobase

Author 1: Adrienne Shnier

Conceived and designed the study, performed the study, interpreted and analyzed the data, wrote the manuscript, and finalized the manuscript.

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Author 2: Joel Lexchin

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I certify that this statement of contribution to the above named paper is correct and give my consent to Adrienne Shnier to include our co-authored manuscript in her doctoral dissertation in partial fulfillment of the degree of Doctor of Philosophy in the Graduate Program of Health at York University.

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Author 3: Mirna Romero

Performed the study, interpreted and analyzed the data, revised the manuscript, and finalized the manuscript.

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Author 3: Mirna Romero

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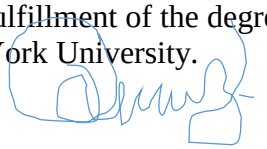
Signed:  Date: July 23, 2015

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Title of Study: Continuing medical education and pharmaceutical industry involvement: An evaluation of policies adopted by 60 Canadian professional medical associations

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