CLINICAL CASE REPORTS AND PATIENTS AS SUBJECTS OF SCHOLARLY ENQUIRY: ONE INSTITUTION'S APPROACH TO ETHICAL AND LEGAL CONSIDERATIONS

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Abstract

Chiropractic case reports that describe the clinical care of one patient or of several patients with similar conditions provide valuable insight to the practicing clinician and offer information for the design of clinical trials. Clinical case studies are not generally subject to federal ethics regulation or review and oversight by research ethics committees protecting human research subjects. Nonetheless, journal editors sometime require authors of clinical case reports to provide proof of evaluation by independent ethics committees. We describe the procedures, guidance, and materials that our institution developed for clinician-authors to obtain ethics documentation and facilitate the publication of their clinical case reports.

Keywords: Chiropractic Case Reports, Ethical Review, Patient Consent

Introduction

Chiropractic case reports that describe the clinical care of one patient, or of several patients with similar conditions or treatments, can provide valuable insight to the practicing clinician, as well as offer information for researchers for the design of clinical trials and other structured research studies (1-5). Case reports are published in medical and chiropractic journals and are often shared as the topic of presentations at chiropractic conferences. Observational reports of clinical interventions conducted primarily for the health of the patient are scholarly activities that generally do not meet official definitions of "research" and as such they do not require ethical review as research projects (6, 7). Although this is not universal, journal editors and conference committees sometimes have publication guidelines (8, 9) that require authors of clinical case reports to provide documentation of ethics approval or a determination that the project does not require ethics review by independent ethics committees for the protection of human subjects (10-13). Even when clinical case studies are not subject to formal ethics review and oversight by human research ethics committees (HRECs), also commonly called Research Ethics Boards (REBs) or Institutional Review Boards (IRBs) (6, 14-16), academic institutions that are committed to supporting ethical conduct of all clinical inquiry and scholarly projects involving human subjects may offer guidance and assistance for academics and clinician-investigators who submit their case reports to journals and conferences that require "ethics paperwork."

Academic institutions that educate health care providers typically operate a teaching clinic within an associated health center, and thereby serve the triadic mission of academic health centers to prepare and train health care providers, to provide health care to their respective communities, and to advance knowledge by conducting research and scholarly activities. Chiropractic colleges and academic institutions that house departments of chiropractic are responsible for oversight and accountability for all aspects of the research enterprise conducted under the auspices of the institutions and their affiliate health centers, including

assurances that all research is conducted ethically and safely, and in accordance with applicable laws and regulations (6, 7). In the U.S., federally-recognized IRBs provide a "Federalwide Assurance" (FWA) of their compliance with federal regulations involving the protection of human research subjects (7, 17).

Offering our own U.S.-based institution as one example: In accordance with our FWA, Life Chiropractic College West maintains an IRB for ethical review of all human subjects research, as well as a research compliance office to make determinations relative to other federal rules and regulations that apply to any clinical research or scholarly enquiry involving patients. Our IRB and research compliance office apply the Common Rule (7) as a framework for reviewing all human subjects research, and for providing ethical guidance to investigators for protecting the rights and well-being of human subjects. Most chiropractic health clinics in the U.S., whether academic teaching centers or private practitioners, must also maintain compliance with U.S. federal law protecting privacy rights of patients, the Health Insurance Portability and Accountability Act (HIPAA) (18). Investigators in the U.S. who conduct research and clinical activities in other countries must apply, at a minimum, equivalent protections provided to research participants inside the U.S. and also comply with international and host country regulations (16, 19). For example, Australian and Canadian regulations address many of the same issues of human subjects research and protected health information as the U.S. Common Rule and HIPAA, with country-specific rules governing oversight of research activities involving the use of patients' health information and human research subjects (15, 20-22).

Differentiating "Clinical Case Study/Series" from "Clinical Research"

Anecdotal case reports, or descriptions of clinical care, are generally not considered to be human subjects research, defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge" (23). However, identifying a manuscript as a "case report" is not always straightforward. While case reports have been defined by some experts as "a detailed narrative that describes, for medical, scientific, or educational purposes, a medical problem experienced by one or several patients,"(13), others write that the literature provides no clear definition and that there is no consensus among authors or journals (5, 24). *IRB Management and Function*, a reference work published by Public Responsibility in Medicine and Research (PRIM&R), an organization that advances ethical research, suggests that anecdotal reports of a course of similar cases should be classified as educational or descriptive activities rather than research regardless of the number of individuals involved. Instead, they say, it is the inclusion of "the basic elements of a systematic investigation of a scientific question" (25), such as pre-determined procedures, statistical methods, subgroup analyses, etc., that qualifies an activity as generalizable research. A review of 586 published clinical studies that were identified in article titles as case reports or case series found that the vast majority of such studies included 1-5 patients, with a median of 4 patients in studies identified as case reports, and a median of 7 in studies identified as case series (26).

At our institution we developed streamlined procedures to expedite the work of our research compliance office and IRB to evaluate clinical case reports and other projects to determine whether they qualify as "research" as defined by the Common Rule and thus subject to ethical oversight (25, 27, 28). In other clinical settings such evaluations may be

performed by internal or external ethics review boards, or even by the clinical investigators themselves (10, 11, 28-31). In addition to describing our own procedures for assisting our clinical scholars as authors of case reports, we include in the supplemental materials to this paper templates and forms similar to those that we provide to support the work of our scholars and clinician-investigators and of those responsible for overseeing compliance of research and scholarly pursuits involving patient care. It is important to note that policies, regulations, and publication conventions change over time. In consequence, we update our forms as needed. Current forms may be obtained from the corresponding author.

Satisfying Journal Publishing Requirements

In December 2016 our Research Department staff searched for submission requirements, ethics review, and examples of patient consent forms from U.S.-based and international English-language journals and conferences that published or presented chiropractic case reports. We discovered that publication policies varied widely; for example of 18 journal and conference websites, only five journals and one conference provided publicly-viewable consent forms or explicit requirements. We used what information we found on the websites, along with our own institutional policies informed by federal regulations, discussions with experts in human subjects protection, and professional and academic standards (9, 14, 23, 25, 27, 30-32) as guidance to develop procedures to support the scholarly work and research efforts of our faculty and students and facilitate their publication of clinical case reports.. However, because there are no uniform publication requirements for case reports, (5, 9), we recommend that authors investigate the requirements of their chosen journal before submitting their case reports for publication.

Patient Consent for Case Report Publication

Informed consent is the cornerstone of ethical clinical research, and it is required for most activities that are determined to be research involving human subjects (6, 32). Even when a clinical case report does not qualify as research, it is commonly accepted that patients' consent for their case to be published should be obtained and documented (9, 12, 13, 33-36). It is wise as well as ethical to obtain patients' consent even when it is not required by the publication venue (34). For example, authors who failed to obtain consent were forced to retract their article when a patient recognized herself even though no identifiers were included in the paper (37, 38). Consent agreements should be clear and explicit; in another retraction the published article stated that the authors had obtained written consent from a deceased patient's family, but the family said they did not give permission for publication (39).

We advise clinical scholars preparing to submit case reports to use any consent forms provided by the publication venue. However, clinicians authoring a case report oftentimes do not know in advance where they will submit their work, or they might decide to write a case report after a patient is no longer under active care. This can make it difficult or impossible to obtain the patient's signature on a journal's own consent form. To assist our clinical investigators, we created a "generic" consent-to-publish form (Appendix 1) that contains those elements we found commonly requested for publication or presentation of case reports. These include name of the author; patient(s) name, signature, and statement of consent; statements that patient has read or has been given the opportunity to read the manuscript being submitted; and notification that patient consent can be revoked at any

time up to acceptance for publication. The form states that while personal identifiers and identifiable photographs will not be published, authors cannot guarantee anonymity.

In addition, we provide authors at our institution with a HIPAA-compliant form for requesting that patients give their signed authorization to access their medical record and protected health information (PHI) or images specifically for the purpose of preparing a clinical case report intended for sharing outside of the institution. Our HIPAA authorization form is particular to our own U.S.-based institution and does not apply to most international research or research conducted entirely in other countries. It is not included among the supplementary materials (but is available on request to the corresponding author). Teaching clinics and private practitioners that are subject to government regulation of healthcare and research (6, 15, 20, 23, 40) typically have their own forms and procedures tailored to the specific characteristics of their patients and settings.

Institutional Ethics Review or Certification

Academic research centers may provide decision trees or other guidance for investigators to self-determine whether or not clinical activities qualify as case reports that do not need to be submitted for ethics review (27, 28, 41, 42). However, in situations where faculty and students do not generally have extensive training or experience as researchers, investigator self-certification might not be the best option. As well, some journal editors or conference committees that rely strictly on publication guidelines (8, 9) may also require "ethics paperwork" from independent ethics committees (10-12, 43). Therefore, at our institution to ensure concordance with professional and ethical standards we provide a process for our investigators to submit their clinical activities for a determination of whether they are case studies which do not require IRB review, or if they qualify as human subjects research, which requires ethics review before any research activities can begin (14). We describe below the institutional process for our clinical scholars to request a clinical case study determination from our IRB or research compliance office.

Case Report Determination Form and Outcome Letter

The "Request for Determination" form (Appendix 2) asks clinical investigators to supply key information (Figure 1) needed to determine whether the proposed activities qualify as a case study/series, or as human subjects research.

Figure 1: Key Elements for Non-Research Case Report Determination

Part 1: Describe Your *Clinical Case Study* or *Clinical Case Series*
In the space below, please describe the clinical activities involved in this Case Study. Include information about the patient(s), such as gender, age, presenting complaint. Describe all clinical assessments, tests, interventions, and treatment protocols that were or will be used in the clinical care and management of the patient(s). Please spell out acronyms the first time they appear. Explain chiropractic, medical, or other terms that might not be familiar to the reader.
Part 2: Please answer the following questions:

1. ☐ Yes ☐ No	Is the clinical activity conducted primarily for healthcare or educational purposes?
2. ☐ Yes ☐ No	Would the clinical activity, i.e. your care for the patient(s) have been provided in the same way, even if the Clinical Case Study (or Clinical Case Series) would never be presented at conference or published in journal?
3. ☐ Yes ☐ No	Is the Case Report retrospective? (i.e., does it involve only the collection or study only of records or documents that were in existence at the time of this application?).
4. ☐ Yes ☐ No	Is the knowledge generalizable? (Generalizable: universally applicable beyond the individuals about whom information is being collected.) Note: A Case Study of 1 patient, or Case Series of 2-to-5 patients, is usually considered "not generalizable."
5. ☐ Yes ☐ No	Does the clinical activity employ any experimental procedures, tests, assessments, imaging, interventions, or devices that have not been approved for use as normal or routine clinical care of such patients at this teaching clinic?

The project description and checklist sections guide the review and determination process. For example, a prospective project or one that includes several patients might require more detail and scrutiny than a single-patient retrospective case report. Because of the explicitly non-experimental nature of the clinical care and education provided in our academic health center, we generally provide our clinical scholars with a determination of "not research" status for descriptive observational case series that include up to five patients. For larger (>5 patients) case series, we advise investigators to consult with our research staff so that we can assist them with submitting, if necessary, a study protocol and application to the IRB for approval of human subjects research. Referencing the checklist in Figure 1, generally a "yes" answer to Items 1-3 coupled with a "no" answer to Items 4 and 5 would predispose the review toward a determination by our institution that the clinical activity is a non-research Clinical Case Study or Case Series that does not require ethics review. However, this is decided on a case-by-case basis.

At our institution, the "Request for Case Report Determination" form is reviewed by a qualified member of the IRB or research compliance office, who will then issue a formal "Letter of Determination" (Appendix 3) on institution letterhead. If the project as described is determined to qualify as "human subjects research," the investigator is instructed to submit a protocol and a study application to the IRB for review and approval. If the clinical activities are determined not to require ethics review, the investigator receives confirmation that the case study is not human subjects research and that the clinical activities described are not subject to IRB oversight. The outcome letter lists the factors that informed the decision and notifies investigators that other regulations (HIPAA, FERPA, etc.) and institutional policies may apply to the project. When applicable, the letter explicitly states that the determination was based on U.S. regulations and therefore cannot be applied to activities conducted elsewhere. Clinical investigators are advised to check with the IRB if they make any changes to the study procedures to be sure the changes do not affect the

study's non-research status. Most journals and conferences that require ethics paperwork for case reports accept such letters (10, 25).

Discussion

There is growing trend to require formal or informal institutional evaluation of case studies and other human subject research activities that are not covered by government regulations (9, 12, 44). Small academic institutions that encourage faculty and students to engage in research sometimes have the added challenge of providing guidance to relatively inexperienced investigators who might be writing a case report for the first time. Clinicians at our institution are encouraged to consult about their projects with our IRB or research compliance office before they begin their case reports. These consultations are optional, but early discussions about their proposed clinical projects can help to avoid potential ethical violations or inappropriate categorization of quasi-experimental n-of-1 or single-subject-time series study designs (35), which do require *a priori* ethics review, as opposed to anecdotal and descriptive clinical reports such as observational case study designs which do not.

To encourage clinical scholarship and interest in careers that include research, students at our institution receive instruction about how to write clinical case reports, their potential evidential value and their position in traditional hierarchies of evidence (1, 45). Classroom activities include writing a sample case report based on their experience as interns in the teaching clinic and a mock-up of a non-human subjects research determination request. Students at our institution who plan to publish their case reports and wish to receive an actual determination are required to work with a faculty mentor, submit *bona fide* documents, and provide certification that they have completed ethics training in protection of human research participants. The faculty mentor must submit the requests for determination on behalf of the student, as the mentor assumes responsibility for oversight of the student's work and for ensuring compliance with applicable rules and regulations.

Similarly, outside clinicians who require ethics paperwork for case reports or research studies have the option to work with faculty investigators at our institution, provided that the affiliated faculty member serves as principal investigator. The unaffiliated investigator must also provide proof of human research subjects protection training, which at the time of this writing is available at no cost (e.g., 46, 47) or through paid sites that offer continuing education credits, membership, and other courses for researchers (e.g., 48, 49-51). Such training programs are generally accepted by institutions in their host countries; investigators conducting research elsewhere are advised to verify that they meet local standards (16) for ethics training. Chiropractors who are not affiliated with institutions that house ethics committees can engage private and non-profit independent IRBs, REBs, and HRECs to provide review services, including case report determinations (e.g., 14, 29, 52-56).

Conclusion

We agree with Haneline that "Case reports are vital to the advancement of knowledge about patient care because they report new or unusual aspects of chiropractic practice that are of interest to and highly relevant to practitioners"(35). Supporting the publication of work by investigators who conduct case studies is a crucial element of the advancement of such knowledge (57). In the absence of universally-accepted guidelines regarding ethics review of case reports (24), we developed policies and procedures that support scholarly

enquiry and are appropriate for our institution, investigators, and regulatory environment. Other institutions and journals around the world have implemented different protocols that meet their particular needs. Whatever the approach, by providing research ethics guidance to investigators regardless of whether there are applicable regulations we can encourage a wide range of scholarly activity, support both novice and experienced investigators in the conduct and dissemination of their work and contribute to the expansion of chiropractic knowledge.

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Appendix 1: Publication Consent Template

(INSTITUTION NAME) Patient Consent for Case Report Publication

Title of submitted case report:

_____

Author(s) name(s):

_____

I understand that my participation in this case study is voluntary; I can choose not to participate in part or all of the project, and I can withdraw at any stage of the project without being penalized or disadvantaged in any way.

The purpose of this study is

_____

_____

_____

As the patient in this case report, I give my consent for clinical information relating to my case to be published in a scientific journal or conference proceedings. I understand that my name, initials, and/or any protected health information such as my identification number, billing information, address, identifiable images, etc. will not be published and that efforts will be made to conceal my identity, but that anonymity cannot be guaranteed. I understand that the material may be published in conference proceedings, a journal, a website of a journal, and/or in products derived from the publication. As a result, I understand that the material may be seen by the general public. I understand that any data collected will be kept in a secure storage area and accessible only to the student or practitioner and their supervisor while the case is being conducted.

Check all that apply:

- ☐ I have been offered the opportunity to read the manuscript to be submitted.
- ☐ I have read the manuscript to be submitted.
- ☐ I consent to publication of the case report.
- ☐ I understand that my consent can be revoked at any time prior to the publication of the manuscript.

_____

_____

Name of patient/guardian Date

_____

Signature of patient (or of the person giving consent on behalf of the patient)

Only complete this section if you are <u>not</u> the patient. (The person giving consent should be a substitute decision maker or legal guardian or hold power of attorney for the person or entity.)

Relationship to Patient:

Why is the person not able to give consent? (e.g., is the person a minor, incapacitated, or deceased?)

_____

_____

Name of Lead Author:

_____

Name of Principal Investigator (if different from Author):

_____

Signature of Author:

_____Date: _____

Signature of Principal Investigator:

_____Date: _____

Note to Authors: Because of patient privacy issues, this form should not routinely be included with the initial manuscript or abstract submission. We recommend the following wording at the submission stage: "We obtained written consent from the patient for publication of this case report and accompanying images (if applicable). A copy of the written consent is available for review upon request by the editors." (or "conference committee," as applicable).

Life Chiropractic College West_2021_ Patient Consent to Publish.Template

Appendix 2: REQUEST FOR CASE REPORT DETERMINATION

This request form should be submitted to (*department name*), to determine whether a proposed Clinical Case Study (or Case Series, if reporting on more than one patient) is considered to be "Not Human Subjects Research", and therefore would not require formal review by the Institutional Review Board (IRB).

A ***Clinical Case Study, reporting*** a retrospective analysis of one patient clinical case, is not generally considered "research" and therefore typically does not require review by the Institutional Review Board (IRB). A ***Clinical Case Series*** *Case Series of up to (# specified by institutional policy)* patients *might* also qualify as "not research", depending on how each patient was selected, and how their patient data is collected and presented in the final scholarly work. Prospective Case Reports *might* also qualify as "not research", depending on how the patients will be identified and selected. For a determination of whether or not your scholarly Case Report project (*Clinical Case Study or Clinical Case Series)* requires IRB review, please provide a description of the patient case(s) in Part I of this form, and answer the questions in Part II. Submit the completed form to *(department email).*

Note: Students may not directly submit IRB Applications or Requests for Determination. These must be submitted by the student's faculty mentor, who agrees to assume responsibility for oversight of the student's work and for ensuring compliance with all applicable rules and regulations, internal and external.

Project Name:	

Author Name/email: _____

Department: _____

Phone: _____

Today's Date: _____

Project Start Date: _____

SUBMITTING AUTHOR: INVESTIGATOR SIGNATURE AND APPROVAL	
By entering my name below, I approve this application as complete and accurate.	
Electronic Signature:	Date:

OTHER PROJECT CONTACT INFORMATION: FOR CO-AUTHOR(S) AND STUDENTS (IF APPLICABLE)	
Co-Author Name/ Email	
Student Name/Email	

Part 1: Use this form or attach a description of your *Clinical Case Study* or *Clinical Case Series*
Please describe the clinical activities involved in this Case Report. Include information about the patient(s), such as gender, age, presenting complaint. Describe the number of patients, all clinical assessments, tests, interventions, and treatment protocols that were or will be used in the clinical care and management of the patient(s). Please spell out acronyms the first time they appear. Explain chiropractic, medical, or other terms that might not be familiar to the reader.

Appendix 3: REQUEST FOR CASE REPORT DETERMINATION

(Institution Name) **Case Report Determination**

Project ID:

To:
From:
Study Name:
Status: Case Study Not subject to IRB Review or oversight.
Date:

The *(Institution and department)* has determined that the case study referenced above is not human subjects research as defined by the US Department of Health and Human Services Code of Federal Regulations 45 CFR 46 as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." As such, the clinical activities involved in the case study are not subject to IRB review or oversight. This determination is contingent upon the following factors:

1. The activities referenced in the report were conducted primarily for educational or healthcare purposes.

2. The activities would have been conducted even if there were no possibility of external publication or presentation.

3. The patient care did not employ any procedures, tests, assessments, imaging, interventions, or devices that would not otherwise be used in the routine clinical treatment for the care and benefit of the patient.

4. The case report is not intended to be generalizable beyond the specific case(s) presented.

Important notes:

- This determination applies only to the case study activities included in this submission.
- If you intend to make changes to the study procedures please check with the *(department)(email)* to be sure they don't affect the study's status.
- Even when an activity is determined not to be human subjects research, HIPAA regulations regarding protected health information of patients, and FERPA regulations regarding the privacy of student information may apply to the activity. Certain clinical procedures, devices, or supplements may require compliance with other regulations. The principal investigator is responsible for ensuring that the project is in compliance with applicable regulations.
- This determination was made in accordance with U.S. federal regulations. For activities conducted outside of the United States, the investigator is responsible for obtaining necessary permissions and ensuring that the activity also complies with local and country ethics rules.

- If you have questions about this determination, please contact me at *(email/phone)*. Please include the Project ID# in all correspondence.

cc:

Life Chiropractic College West Case Report Determination Letter.Template.v2