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Dear Dr. Cassady-Cain,

I appreciate your considering our manuscript for publication. Allow me to provide the clarification you requested regarding our ethics/consent policy.

Our observational study falls under the Helsinki Guidelines definition of clinical research.[1] All physicians who voluntarily participated in the study understood that they were using a new test in development and that the data they were using to help make their own clinical decisions would also be used for this study. Unlike

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[1] **Medical Research Combined with Professional Care (Clinical Research)**

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient- including those of a control group, if any- should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge,only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

   - World Medical Organization. Declaration of Helsinki. *British Medical Journal* 1996;**313**:1448-1449.

randomized controlled trials, however, no experimental interventions were performed on the patients in this study. We simply provided doctors with educational material in the form of a test. The educational material recommended choices between approved medications, any of which might have been used routinely under existing U.S. Food and Drug Administration guidelines. Physicians were free to follow the recommendations or not and were encouraged to use their own judgment in the care of all patients. We processed and collected test score data online to monitor the effects of the educational material on patient outcomes. By analogy, it would be similar to collecting patient data to identify journal articles that might help doctors improve patient care and then monitoring outcomes between physicians who read articles versus those who didn't. We agree with those who assert that, when no potential harm to patients exists in an observational study, it is inordinately costly and obstructive to the goals of science and public health to require investigators to go through procedures designed for research that does subject patients to potential risks.[2]

There are precedents in several countries for exemptions from strict Helsinki-based requirements. Our study falls within the guidelines for one such set of exemptions as stated in U.S. Federal Regulation 45 CFR 46.101(b).[3]

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[2] Orchard J: **For debate: Should observational clinical studies require ethics committee approval?** *Science and Medicine in Sport* 2008; **11**:239-242.

[3] **Categories of Exempt Research found at Federal Regulation 45 CFR 46.101(b)**
(educational research document modified for analogous medical/psychological settings)
(1) Research conducted in established or commonly accepted medical settings, involving normal medical practices, such as (i) research on regular and special health treatment strategies, or (ii) research on the effectiveness of or the comparison among treatment techniques, strategies, or health management methods.
(2) Research involving the use of psychological tests (cognitive, diagnostic, aptitude, achievement), survey
procedures, interview procedures or observation of public behavior, unless:
i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
(3) Research involving the use of psychological tests (cognitive, diagnostic, aptitude, achievement), survey
procedures, interview procedures, or observation of public behavior that is not exempt under paragraph
(b)(2) of this section, if:
(i) The human subjects are elected or appointed public officials or candidates for public office; or
(ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

As stated in the paper, we also observed HIPAA guidelines to protect patient identity.[4]

In Australia, according to Orchard (cited above), "the latest (2007) National Health and Medical Research Council (NHMRC) of Australia policy on Human Research does not require universal ethics approval for all human studies, defining a 'low risk' study (one not requiring HREC (Human Research Ethics Committee) approval) as one where the only foreseeable risk is one of 'discomfort'." For the patients whose test scores were included in this report, the "discomfort" of completing a brief questionnaire was the only potentially adverse experience compared to treatment as usual.

Two last points: (1) Limiting an observational study of depression to the results derived only from patients willing to provide "informed consent" for approved treatments from their own doctor is itself a distorting factor. It might skew the data

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[4] **HIPAA Privacy Rule Standard for De-identification found at 45 CFR 164.514(b):**
The following identifiers of the individual or of relatives, employers, or household members of the individual, are removed:
(A) Names;
(B) All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
(1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
(2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
(C) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
(D) Telephone numbers;
(E) Fax numbers;
(F) Electronic mail addresses;
(G) Social security numbers;
(H) Medical record numbers;
(I) Health plan beneficiary numbers;
(J) Account numbers;
(K) Certificate/license numbers;
(L) Vehicle identifiers and serial numbers, including license plate numbers;
(M) Device identifiers and serial numbers;
(N) Web Universal Resource Locators (URLs);
(O) Internet Protocol (IP) address numbers;
(P) Biometric identifiers, including finger and voice prints;
(Q) Full face photographic images and any comparable images; and
(R) Any other unique identifying number, characteristic, or code; and (ii) The covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information.

towards results from those people who are free enough from anxiety or hopelessness to overcome such a barrier; (2) Obtaining outside funding (e.g., from a pharmaceutical company) to afford paying for a private ethics committee review would have subjected the data to potential control by entities with a history of limiting or influencing published data.[5]

For the above reasons, we believe that this study was not only ethically conducted, but that it also provided a more accurate representation of clinical practice. We would be glad to make a brief statement about the reasons for this exception in the methods section if requested.

Sincerely,

Richard J. Metzner, M.D.

[5] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R: **Selective publication of antidepressant trials and its influence on apparent efficacy.** *N Engl J Med* 2008, **358**:252-260.