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Hidden Empirical Research Ethics: A Review of Three Health Journals from 2005 through 2006

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Abstract

We hypothesized that a significant amount of empirical data pertinent to research ethics is currently inaccessible to research ethics committee or Institutuional Review Board (IRB) members for at least three reasons: it is published in non-ethics journals; articles are not adequately indexed using ethics-related keywords; and articles do not discuss the ethical significance of their data. We reviewed all articles from three health journals from January 2005 to December 2006, and identified 26 articles that contained data pertinent to research ethics. Only 7 articles contained keywords clearly related to research ethics; 15 of the articles contained no discussion of the ethical significance of their findings. Overall the articles we found constituted 2.2% of the research articles published in the three journals during the two-year period. If the same average number of articles were extrapolated to the top 100 of the approximately 5,000 journals indexed in MEDLINE, then at least 433 hidden ethics articles would be published each year. We conclude that better indexing of articles is needed, that IRB members and researchers need training to identify relevant data in the literature, and that IRB composition should include members from diverse disciplines familiar with ethics-relevant empirical data in their respective disciplines.

Keywords

research ethics; review article; institutional review boards; human experimentation; vulnerable populations

Various investigators (e.g., Roberts,2000; Sieber, 2004) have called for the development of "evidence-based" research ethics, recognizing that many assumptions made about participants and protections are based more on prejudice, hunch, or anecdote than on data. Numerous ethical questions simply cannot be answered without the use of empirical data. This basic insight provided the primary motivation for the development of the *Journal of Empirical Research on Human Research Ethics* (*JERHRE*). *JERHRE* was established to provide a home for those who wish to publish empirical data in this fledgling field. Such a niche journal may serve at least two different purposes. First, it may provide a publication outlet for important work that currently falls outside the purview of most other journals, and therefore is difficult to publish. Second, it serves to consolidate articles in a specific field, thereby making it easier to locate relevant articles, providing visibility to a field of inquiry, and bringing scholars (authors, reviewers, editors, and readers) together in a collaborative manner.

Nevertheless, empirical data on research ethics are still published in other journals—sometimes other ethics journals, but commonly in journals serving specific disciplines such as medicine, public health, or psychology. This is excellent insofar as such publications may reach a wide

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number of readers working in a discipline, and not just those who are particularly concerned with research ethics. However, such data may remain hidden precisely from those individuals who craft research policies, review research protocols, and teach research ethics. When this occurs, the risk arises that IRB recommendations and research ethics education will fall back on the "hunches and anecdotes" that provide such poor substitutes for trustworthy data.

DuBois (this issue) identifies three senses in which scientific data on research ethics may be hidden from the view of Institutional Review Board (IRB) members and ethicists:

1. The data are not published in a journal dedicated to empirical ethics or research ethics such as: *Accountability in Research; Ethics and Behavior; IRB: Ethics & Human Research*; or *JERHRE*.
2. The article in which data appear does not identify directly relevant keywords such as "research ethics" or "research" combined with terms like "informed consent," "confidentiality," "justice," and "conflicts of interest," thus reducing the likelihood of successful database searches.
3. The authors do not discuss the ethical implications of their data.

This article aims to determine the prevalence of hidden data pertaining to research ethics by examining a purposive sample of scholarly journals that focus on research with a vulnerable population during a recent two-year period, 2005–2006. We selected leading journals that focus on research with vulnerable populations because such research is typically viewed as raising special ethical concerns due to participants' compromised ability to protect themselves (DuBois, 2005; Kipnis, 2001). Thus, it seemed reasonable to hypothesize that such journals would be receptive to publishing articles that address ethical dimensions of human research.

Methods

DATA SOURCES

The journals *AIDS*, *American Journal of Psychiatry*, and *Pediatrics* were searched over a two-year time span (January 2005–December 2006) for articles that met the inclusion criteria.

PROCEDURES

Two of the authors (RV & ER) independently read the title, abstract, and keywords of each article published in the three journals during the specified publication dates. Only original empirical papers were included in further review. If an empirical study appeared to address a research ethics theme or if it contained a finding that was potentially relevant to research ethics, then the full text article was examined for further evaluation.

Research ethics topics were defined using the framework provided by Emanuel, Wendler, and Grady (2000). Based on their critical examination of thirteen national and international codes of ethics, Emanuel et al. outlined seven requirements for ethical clinical research studies: (1) value, (2) scientific validity, (3) fair subject selection, (4) favorable risk-benefit ratio, (5) independent review, (6) informed consent, and (7) respect for enrolled subjects. We chose this framework because it analytically distills the consensus regarding research ethics that is reflected in multiple national and international codes of ethics.

After reviewing all of the articles separately, the two reviewers met to discuss the possible inclusion of each article. In many cases, the reviewers had chosen the same articles for inclusion; where they did not, they discussed their rationale and consulted with the third author (JD) to achieve a consensus. Finally, all three authors met to review all prospective articles to ensure that they met the review criteria and that no articles were inappropriately excluded.

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Articles that were selected for inclusion presented empirical data relevant to understanding at least one of the seven requirements for the ethical conduct of research. These articles were analyzed with three questions in mind:

1. Which of the seven requirements for the ethical conduct of research are better understood in the light of the data?
2. Do the keywords of the article include either ethics terms, such as *ethics*, *bioethics*, or *research ethics*, or related terms such as *informed consent*, *recruitment*, or *confidentiality*?
3. Do the authors discuss the ethical significance of their findings?

Results

Twenty-six articles were selected for inclusion: seven from the journal *AIDS*, ten from the *American Journal of Psychiatry*, and nine from *Pediatrics*. See Tables 1, 2, and 3 for a summary of each article. The seven articles from *AIDS* represented 2.22% of all the research articles published in that journal over the two-year time frame, the ten articles from the *American Journal of Psychiatry* represent 3.75% of all the research articles published in that journal over our specified time frame, and the nine articles from *Pediatrics* represents .667% of all research articles published in that journal.

The 26 articles were "hidden," according to our definition in various manners. All 26 articles appeared in a non-ethics journal. Seven of the articles included an ethics keyword; 12 included a keyword only indirectly related to research ethics (e.g., "recruitment"); and 7 contained no keyword related to ethics. Eleven of the articles discussed the ethical significance of their findings; 15 did not.

Our presentation of the articles is broken down using the seven requirements for ethical clinical research provided by Emanuel, Wendler, and Grady (2000): informed consent; respect for enrolled subjects; value; scientific validity; fair subject selection; favorable risk-benefit ratio; and independent review. We found articles in every category except "independent review."

INFORMED CONSENT

Informed consent requires provision of information to subjects about the purpose of the research trial, its procedure, potential risks, benefits, and alternatives. For consent to be valid, individuals must understand and appreciate the information conveyed and be free of coercion. Only then can individuals weigh their options and make a voluntary and informed decision whether to enroll in the trial (Emanuel et al., 2000).

Brody, Scherer, Annett, Turner, and Dalen (2006) examined parent and adolescent perceptions of decision-making authority and sources of influence on adolescent research participation decisions. Thirty-nine adolescents and their parents reviewed nine research protocols and then answered a series of questions about each. Results showed that adolescents were less willing to cede decision-making authority to parents than parents anticipated. The authors conclude that researchers, physicians, and institutions play an important role in facilitating the ethical enrollment of adolescents in research.

Prentice, Gold, and Carpenter (2005) investigated whether patients with schizophrenia demonstrated optimistic biases in their perceptions of personal risk at an equal or different rate than non-ill, matched adults. If so, this optimistic bias could interfere with the ability to give informed consent in research and treatment settings. The authors found that both groups showed an optimistic bias in general, and that non-ill comparison subjects demonstrated a greater level

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of optimism than schizophrenia patients. They conclude that although patients with schizophrenia are not at an increased risk for misperceptions of personal risk, the larger concern surrounding healthy adults' ability to give fully informed and rational consent in clinical settings still exists.

Jollant et al.'s (2005) study examined the decision-making capacity of people who attempted suicide. The authors used a standardized decision-making assessment task to investigate patients with a history of violent or non-violent suicidal behavior, patients suffering from affective disorders with no history of suicidal behavior, and healthy comparison subjects. They found that both groups of suicide attempters scored significantly lower than healthy comparison subjects on decision-making capacity, and violent suicide attempters performed significantly worse than affective-disorder comparison subjects. These data suggest that special attention should be paid to suicide attempters seeking to participate in clinical research, as their decision-making capacity may be impaired.

Lee, Havens, Sato, Hoffman, and Leuthner (2006) explored clinician knowledge, attitudes, and practice regarding assent for medical treatment in children. A questionnaire was administered to 35 clinicians, and the results showed that clinicians tend to lack a robust understanding of assent. Specifically, 66% of clinicians had heard the term "assent" and only 35% understood seeking the child's agreement to be a goal of the assent process (suggesting they had very weak understandings of what it means to engage in an assent process with children). These research findings are interesting both in terms of clinical treatment as well as research in children.

Ordinarily, when a participant loses the capacity to grant informed consent, they cannot participate in research except when a waiver of consent can be granted or local law allows consent for research to be granted by a proxy. However, the use of "advanced directives" for research participation has been suggested as one way to allow individuals to express choices regarding future research participation while they still have decisional capacity. Muthappan, Forster, and Wendler (2005) assessed how many adults completed a research advanced directive and the preferences indicated on the completed form. Overall, only 11% of potential or current research subjects completed a research advanced directive, even after being explicitly encouraged to do so. The authors also found that 13% of subjects who filled out the form checked the box stating that they were not willing to participate in research should they lose the ability to consent, 49% stated they were willing to participate in research that "will not help me but might help others and involves no more than minimal risk to me" and 9% checked the box that stated they were willing to participate in research that "will not help me but might help others and involved greater than minimal risk to me."

Kimberly, Hoehn, Feudtner, Nelson, and Schreiner (2006) compared standards for compensation and child participant assent in the permission, assent, and consent forms approved by 55 IRBs. The authors found that compensation ranged widely within and across studies, and that procedures for obtaining child assent and informed permission also varied widely across studies.

RESPECT FOR ENROLLED SUBJECTS

Emanuel et al. (2000) identify five essential ways of respecting enrolled study participants: (1) permitting subjects to withdraw from the research at any time, (2) protecting privacy through confidentiality, (3) informing subjects of any newly discovered risks and/or benefits, (4) informing subjects of results of the clinical trial, and (5) maintaining the welfare of the subjects. We found two articles that fall within this category of respect for enrolled subjects.

Dunn, Palmer, Keehan, Jeste, and Appelbaum (2006) investigated the degree to which older schizophrenia patients manifest beliefs reflecting the therapeutic misconception. Using a

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hypothetical double-blind placebo controlled trial as a stimulus, the authors examined the frequency of key aspects of therapeutic misconception with a true/false scale in 87 schizophrenic individuals. The authors found that, as in studies of other mental illness populations, patients with schizophrenia show a substantial incidence of beliefs associated with therapeutic misconception; only 31% of participants were characterized as "therapeutic misconception absent."

Moser et al.'s (2005) study aimed at determining whether people with schizophrenia experience changes in decisional capacity when their antipsychotic regimens are discontinued for research purposes. All participants who demonstrated adequate understanding of study procedures at enrollment, however, retained this capacity throughout the study, demonstrating that participants in medication-free schizophrenia research do not show major decline in decisional capacity. This determination is important to ensuring that schizophrenia research subjects can truly provide informed consent, as well as making certain that this population is not neglected in research due to concern related to their decisional capacity.

VALUE

According to Emanuel, Wendler, and Grady (2000), in order to be ethical, clinical research must be of social or scientific value in that it either evaluates a diagnostic or therapeutic intervention that could lead to improvements in health or well-being, or it contributes knowledge that seems likely to lead to the development of such an intervention. In addition to the importance of general social or scientific value, we also believe ethical clinical research should be of value to individual participants by offering a meaningful benefit whenever possible. We found one article that addressed *value* in human research ethics.

Mental health services research is unable to blind participants to their experimental condition. In this regard, such research is susceptible to bias if participants strongly like or strongly dislike their experimental condition (e.g., being assigned to receive mental health services from a mobile service center or rather in a facility-based day program from 9am–5pm). Macias, Barreira, Hargreaves, Bickman, Fisher, and Aronson (2005) conducted a study that explored the relationship between the value a study has for individual participants and the quality of their participation in the study. They examined the potential for research participants' preference for one experimental group over another to compromise the generalizability and validity of randomized controlled mental health service evaluations. The authors measured the impact of applicants' service assignment preference on research project enrollment, engagement in assigned services, and a service-related outcome, competitive employment (defined as any job located in a mainstream, integrated setting paying at least minimum wage and lasting more than five days). A match to service assignment preference was a significant positive predictor of service engagement; and mismatch to assignment preference was a significant negative predictor of both service engagement and employment outcome. The results of this study suggest that referral source type and service assignment preference should be routinely measured and statistically controlled for in all studies of mental health service effectiveness to provide a sound empirical basis for evidence-based practice. In addition to evaluating an issue of value for participants, this study also contributes data pertinent to the scientific validity of mental health research.

SCIENTIFIC VALIDITY

In order for research to be scientifically valid, accepted scientific methods and principles must be followed. For example, the research must be feasible and clinical studies that compare two treatments must have a valid null hypothesis such as: the experimental drug is no different from placebo (Emanuel et al., 2000). This ethical requirement is closely related to the requirement of "value" because studies that lack scientific validity cannot provide value. In this sense, all

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of the articles identified under this heading also related to "value." We found a number of studies that generated data relevant to understanding scientific validity.

Anttila, Malmivaara, Kunz, Autti-Ramo, and Makela (2006) reviewed and evaluated the reporting of data from research on physiotherapy interventions in children with cerebral palsy. The authors found that only a small number of trials reported results sufficiently, based on the principles advocated by the Consolidated Standards of Reporting Trials (Begg et al., 1996; Altman et al., 2001). These principles were developed to assist readers of the medical literature in determining the quality of a study's data. They found inadequate reporting of the following items: outcome measures, sample-size determination, details of the sequence generation, allocation concealment and implementation of the randomization, success of assessor blinding, recruitment and follow-up dates, intention-to-treat analysis, precision of the effect size, co-interventions and adverse events. The authors conclude that there is a clear need to improve the quality of reporting of trials in childhood cerebral palsy interventions.

Brahan and Bauchner's (2005) goal was to analyze whether studies of health disparities are methodologically sound, and to examine some demographic variables that are likely predictive of these disparities. They describe the reporting of race/ethnicity and socioeconomic status, in comparison with age and gender, and to report changes in time. To achieve these ends, they reviewed several journals for two time periods: 1991–1993 and 2000–2002. They found that between the two study periods there were significant increases in studies reporting race/ethnicity, but not in studies reporting gender or socioeconomic status. The authors concluded that if we are to understand health disparities, then more appropriate and complete reporting of socioeconomic status and race/ethnicity is required. Insofar as such data reporting would also enable us to assess the representation of different groups in research, it might be relevant to "fair subject selection" as well.

Polsky, Doshi, Bauer, and Glick (2006) identified eight studies through a MEDLINE search that analyzed the cost-effectiveness of second-generation antipsychotics relative to first-generation antipsychotics in individuals with schizophrenia disorders. They found that generally the authors recommended second-generation antipsychotics, but methodological flaws threatened the validity of the results that formed the basis of the recommendations. Polsky et al. conclude that clinicians and researchers should consider methodological issues when interpreting study results.

The transmission of drug-resistant HIV is a major concern. Identifying drug-resistant strains of HIV is important in clinical trials because they are likely to affect the efficacy of antiretroviral therapy. Yet standard sequencing techniques may be inadequate to identify all individuals with drug-resistant strains. Individuals infected with HIV often have more than one serotype, and methods used to identify an individual's serotype makeup have relied upon sequencing techniques for genotypic analyses that do not allow quantification of minority viral populations below 25%. Menzer et al. (2005) evaluated the prevalence of drug resistant HIV-1, with an emphasis on identification of drug-resistant variants as a minor viral species in acutely HIV-infected patients. They found that drug-resistant variants were detected in 10 of 49 patients, and 5 of the 10 had minor viral quasi species (<25% of viruses). Thus, a small but detectable group of people (those with low viral loads) are not being separated out from others in research studies, potentially confounding results.

Calleja et al. (2005) examined survey techniques for assessing HIV prevalence among households in Mali, Kenya, Peru, and Zambia. The authors concluded that with careful planning and increased financial and human resource investment to maximize response rate, reliable and useful results can be obtained through surveying methods, and that participation rates are higher when less intrusive testing methods are used (e.g., testing saliva rather than

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blood samples). Their conclusions are also relevant to the assessment of perceived "risk/benefit" ratios because they found participant preferences for less intrusive tests.

Gandhi et al.'s (2005) review of phase II and III clinical trials for patients with HIV examined the applicability of a subset of 32 NIH-funded clinical trial results to real-world situations based upon the comparability of trial participants to the general patient population. They examined the characteristics of a representative cohort of HIV positive women (in the Women's Interagency HIV Study) and found that on average the exclusion criteria in the 32 clinical trials would have excluded 42% of these women. Gandhi et al. also state that significant under-reporting of the full list of HIV enrollment criteria in publications may lead readers to believe the trials are more generalizable than they really are to the real HIV infected population. Their conclusions are also relevant to fair subject selection, because it appears that many stakeholders are being excluded from participation in clinical trials.

FAIR SUBJECT SELECTION

Emanuel et al. (2000) identify fair subject selection as the "selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research" (p. 2703). We used a broad interpretation of Emanuel's concept of fair subject selection to refer to any prejudicial treatment of groups, for example, under-inclusion of stigmatized people. We found six articles that fit into this category. Wolitski et al. (2005) note that at present there are few rigorously evaluated risk-reduction interventions for individuals living with HIV, partly out of concerns about feasibility. The authors' original study examined the participation and retention rates of HIV positive and bisexual men in assessments and HIV prevention sessions. Of the 1168 men who completed the baseline assessment, 95% opted for sexually transmitted infection (STI) testing and of the 811 who attended the first intervention session, 85% returned for a three-month assessment, and 90% for a six-month assessment. This study demonstrated the feasibility and acceptability of intervention research with HIV-positive gay and bisexual men, a group that has been largely neglected in transmission prevention research efforts.

Storosum et al. (2005) investigated whether there is a greater suicide risk in the placebo arms of placebo-controlled studies of active medication for the treatment of acute manic episodes and the prevention of manic/depressive episodes. By reviewing 11 placebo-controlled double-blind studies of the treatment of acute manic episodes, the investigators found that there was no increased risk for suicide among the placebo arms of these studies. These results suggest that concern about greater risk of suicide or attempted suicide in the placebo group should not be an argument against the conduct of placebo-controlled trials of treatment for manic-depressive episodes. This study is also relevant to favorable risk-benefit ratio.

Parkes, Kerr, McDowell, and Cosgrove (2006) assessed recruitment bias in a population-based study of locomotor ability in children with cerebral palsy. The authors note that systematic differences in the characteristics of those participating in research compared with those who do not participate have been shown to include clinical, social, and ethnic biases. Their study aimed to quantify these differences. Ultimately, however, their method employing case registers showed no evidence of any systematic biases in demographic or key clinical characteristics. The authors conclude that case registers can make a valuable contribution to clinical research by providing a sampling frame including information on baseline characteristics of an affected population. This study is also relevant to informed consent.

Zamani et al. (2005) interviewed drug users who visited three public drug treatment centers in Tehran and tested them for HIV-1. The strongest predictor (adjusted odd ratio of 12.37) among the HIV-positive males was sharing needles in prison. Given that IRB approval of medical research with prisoners generally requires that the research investigate conditions particularly

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affecting prisoners as a class [45CFR46.306(a)(2)(iii)], this study thus justifies research on intravenous drug users in prison.

Wools-Kaloustian et al. (2006) conducted a study on the clinical and immunological outcomes of antiretroviral therapy for people with HIV to see whether it is justifiable to exclude some people with HIV from research because of difficulties with retention and adherence to treatment programs. They found that although 24.5% of the subjects were lost to followup, 86% of those who remained reported perfect adherence to their treatment regimen. They concluded that large-scale HIV treatment in resource-limited settings should be considered viable and effective. Individuals and communities with limited resources are often excluded from studies because researchers believe that it will be difficult to retain them as subjects. Wools-Kaloustian et al.'s study shows that research is feasible with this population.

Research with children, as well as screening programs, are often delayed or terminated because of concerns about adherence to the treatment regimen among children. Brassard, Steensma, Cadieux, and Lands (2006) evaluated a school-based screening program that targeted children at high risk for TB infection in Montreal. In Canada, there is no systematic screening for latent TB infection among newly-arrived immigrant children. Their method was a retrospective review of available data based on examination of cost-effectiveness and adherence rates. They found that of the children tested, 21% tested positive on the tuberculin skin test, and 92% of those children demonstrated adequate adherence to medication. This study shows a very high rate of adherence among children, thus providing evidence that children can be effective participants in research and screening programs.

FAVORABLE RISK-BENEFIT RATIO

For clinical research to be ethical, risks should be minimized and benefits maximized. Furthermore, the risks to the subject should be proportionate to any benefits the subject and society may gain (Emanuel et al., 2000).

Roberts, Hammond, and Hoop (2006) attempted to clarify how people with schizophrenia evaluate the potential harms associated with various research-related procedures and how these assessments relate to participation willingness. They found that rated willingness to participate was inversely related to the participants' perceptions of harmfulness for all procedures, thus showing that the people with schizophrenia perceive research risk in much the same manner as people without schizophrenia.

Gardner et al. (2005) assessed whether intervention by a case manager improves the care for persons who recently received an HIV diagnosis. The results showed a higher proportion of case-managed participants visiting an HIV clinician at least once within 6 months (78% vs. 60%) and at least twice within 12 months (64% vs. 49%). The authors conclude that a brief intervention by a case manager was associated with a significantly higher rate of successful linkage to HIV care. While the authors recognize this method to be an effective resource in the treatment of HIV patients, the study also has implications for providing research subjects with a more favorable risk/benefit ratio and increasing retention and the generalizability of data (by providing a brief case manager intervention).

Iltis, DeVader, and Matsuo (2006) examined current payment practices in pediatric research by reviewing clinical trial articles published in the journal *Pediatrics* and surveying their authors. Iltis and colleagues found that both payment practices and the reasons for adopting certain payment practices varied. They also found that while the number of institutions with *payment policies* for pediatric research has increased, it still comprises only half of institutions involved in pediatric research. Finally, they found that while authors of articles generally claimed that they do not increase rates of payments to accommodate the level of risk, in fact,

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higher risk studies correlated with higher payments. The authors assert the need for further research in order to build consensus and develop national guidelines. This study is also relevant to fair subject selection and informed consent.

Meyer, Ritholz, Burns, and Truog (2006) empirically identified and described parental priorities and recommendations in end-of-life care for their children. Parents identified six priorities for pediatric end-of-life care: (1) honest and complete information, (2) ready access to staff, (3) communication and care coordination, (4) emotional expression and support by staff, (5) preservation of the integrity of the parent-child relationship, and (6) their personal faith as a resource. Their data provide IRBs with benchmark data in determining the extent to which a study might foster or interfere with what parents consider gold standard end-of-life care.

INDEPENDENT REVIEW

Independent review by individuals unaffiliated with a clinical research project minimizes the potential impact of conflicts of interest in determining research protections and consent procedures and it may encourage social accountability. This requirement for ethical human subjects research is most commonly achieved in the United States through granting agencies, local IRBs, and data safety and monitoring boards. We found no articles related to this research ethics topic.

OTHER

Beyond the seven requirements for ethical research identified by Emanuel, Wendler, and Grady (2000), we found the need to include an “other” category to accommodate conflicts of interest.

Perlis et al. (2005) investigated the prevalence and implications of industry sponsorship and financial conflicts of interest in psychiatric clinical trials. The authors examined 397 clinical trials, their funding sources, and the results of the trials. Sixty percent reported receiving funding from a pharmaceutical company or other interested party; 47% included at least one author with a reported conflict of interest. Articles in which authors reported a financial conflict of interest were 4.9 times more likely to present positive results than when authors did not report conflicts of interest.

Discussion

We hypothesized that empirical data relevant to research ethics would be found in non-ethics journals, sometimes without the use of “ethics” keywords, and sometimes without discussion of the ethical significance of the data. These hypotheses were confirmed.

We admit that the selection of articles for inclusion was a subjective process; other reviewers might have included additional articles, excluded some that we reviewed, or categorized some of the studies differently. While the connection between data and research ethics is tight and intuitive in some articles we reviewed, it is admittedly looser and less intuitive in other instances. However, our methodology and findings are sufficient to support the claim that much of the empirical data relevant to addressing questions of research ethics lies hidden from the view IRB members and research ethicists. In the three journals we examined, we found “hidden” 26 ethics-related articles over a two-year period. This was an average of 2.2% of the research articles published in these journals.

The US National Library of Medicine states that the MEDLINE database currently indexes approximately 5,000 journal titles (of an estimated 13–14,000 biomedical journals).[1] If the same number of articles were found in, say, just the top 100 biomedical journals, then the result would be 433 such articles per year. While some journals may have much lower rates of

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publishing ethics-related articles, there are also far more than 100 biomedical journals (at least 4,900 more that are indexed)—so this figure may not be far-fetched. In short, it is likely that far more articles relevant to research ethics are "hidden" than are published in all ethics journals that focus on empirical ethics or research ethics.

Best Practices

Best practices implied by our findings include ways of reducing the prevalence of hidden data relevant to research ethics and ways of addressing questions of research ethics even while much of the best data remains hidden.

The fact that much empirical data relevant to research ethics is published outside of ethics journals does not present a problem when "ethics" keywords are used. Authors, editors, and indexing librarians should become familiar with appropriate ethics keywords and should be trained to recognize ethically significant data. This would significantly reduce the likelihood that valuable data will be buried and left unused by all but a few.

The findings in this article reinforce the commonly held belief that IRBs need representatives from a variety of disciplines, in particular, people who are familiar with their own peer-reviewed literature. For example, HIV, pediatric, and psychiatric researchers are more likely to be familiar with the content of the articles we reviewed than others. Moreover, because researchers in specific disciplines are more likely to be familiar with their own literature than the average IRB reviewer, researchers should draw from data in their disciplines as they explain in IRB protocols how they will address the various requirements for the ethical conduct of research.

Research Agenda

Research on the phenomenon of "hidden research ethics" may take one of two general paths, as illustrated by the articles in this issue. On the one hand, research may investigate how prevalent data relevant to research ethics are in non-ethics journals by expanding the range of journals and the years of publication reviewed. One might also examine the keywords that would need to be used to capture a majority of such data, and examine how many "false positives" keyword searches produce using merely "related terms" (such as "research methods" or "recruitment"). On the other hand, researchers may explore specific topics—e.g., aspects of the seven requirements for the ethical conduct of research—drawing from data in a wide variety of fields. This study suggests that such research, if it is to be evidence-based and comprehensive, must consult literature published in non-ethics journals, including inadequately indexed studies. Both kinds of basic research are needed.

Whether categorized as research or as a professional service, the field of research ethics would be well-served if *JERHRE* or another suitable research ethics journal regularly published general or thematic annotated bibliographies of empirical studies that are in some fashion "hidden" from most IRB members. (Editor's note: Submission of such research would be welcomed!)

Educational Implications

Ethics education should focus on increasing sensitivity to ethical issues and how empirical data may be relevant to various ethical principles and problems. "Ethics data" are all around us if we are only trained to recognize them.

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[1]The National Library of Medicine discusses MEDLINE and its indexing system at http://www.nlm.nih.gov/pubs/factsheets/j_sel_faq.html#a14. Last visited June 8, 2008.

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IRB members, research ethicists, researchers, and policy makers should be trained on how to find empirical data pertaining to research ethics. This involves not only consulting specialty journals like *JERHRE*, but conducting literature reviews using a broad array of keywords, snowballing from reference lists, and consulting with peers who are familiar with the empirical literature in specific fields of inquiry.

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TABLE 1

Hidden Empirical Data on Research Ethics from *AIDS* (2005-2006).

Author/Date	Population/Data Source	Conclusion	Ethical Issues	Ethics Keywords	Explicit Ethics Discussion
Wools-Kaloustian et al. (2006)	HIV-positive non-pregnant adult patients treated with antiretroviral drugs (n = 2059)	Large-scale HIV treatment in resource-limited settings should be considered viable and effective.	Fair subject selection	No	No
Calleja et al. (2005)	Review of national, population-based HIV surveys (n = 4)	Reliable and useful results can be obtained, although they require increased planning and financial and human resources.	Favorable risk-benefit ratio; scientific validity	No	No
Gandhi et al. (2005)	Review of NIH-funded HIV randomized controlled trials in phases II and III (n = 32)	Significant underreporting of the full list of HIV enrollment criteria in publications, and certain populations being excluded from research may impact the generalizability of these trials.	Scientific validity	Related terms	No
Menzer et al. (2005)	Acute HIV seroconverters from two clinical centers in Germany (n = 29)	The prevalence of minor populations of drug-resistant HIV-1 in acute seroconverters can be frequently detected and may impact the success of antiretroviral therapy.	Scientific validity	No	No
Zamani et al. (2005)	Drug users who visited three public drug treatment centers in Tehran (n = 611)	Shared injection inside prison is a particular risk factor for HIV-1 infection among drug users.	Fair subject selection	No	No
Wolitski et al. (2005)	HIV-positive gay and bisexual men (n = 1168)	Gay and bisexual men can commit to HIV prevention and intervention sessions and assessments.	Fair subject selection	No	No
Gardner et al. (2005)	Recently diagnosed HIV patients in Atlanta, Baltimore, Los Angeles, and Miami (n = 273)	Brief intervention by a case manager was associated with a significantly higher rate of successful linkage to care.	Favorable risk-benefit ratio	No	No

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TABLE 2

Hidden Empirical Data on Research Ethics from the *American Journal of Psychiatry* (2005-2006).

Author/Date	Population/Data Source	Conclusion	Ethical Issues	Ethics Keywords	Explicit Ethics Discussion
Roberts, Hammond, & Hoop (2006)	People with schizophrenia (*n* = 60)	People with schizophrenia perceived the potential harms associated with research procedures in a manner that was logical and clear.	Favorable risk-benefit ratio	Yes	Yes
Polsky et al. (2006)	Studies comparing cost-effectiveness of first- versus second-generation antipsychotics in individuals with schizophrenia (*n* = 8)	Generally, studies recommend second-generation antipsychotics, but unstated methodological flaws threaten the validity of the study results.	Scientific validity; value	Related terms	No
Muthappan, Forster, & Wendler (2005)	Adults admitted as inpatients to the NIH Clinical Center from March 14 to September 13, 2000 (*n* = 2,371)	Only 11% of potential or current research subjects completed a research advanced directive, even after being encouraged.	Informed consent	Related terms	Yes
Prentice, Gold, & Carpenter (2005)	Schizophrenic outpatients (*n* =25) and healthy comparison subjects (*n* = 23)	Both groups showed optimistic bias, however healthy comparison subjects demonstrated a greater level of optimism.	Informed consent	Related terms	Yes
Dunn et al. (2006)	Patients diagnosed with schizophrenia or schizoaffective disorder, age >50 (*n* = 87)	Patients with schizophrenia show a substantial incidence of beliefs associated with therapeutic misconception.	Informed consent	Yes	Yes
Perlis et al. (2005)	Clinical trials from four general psychiatry journals (*n* = 873)	Those studies that reported conflict of interest were 4.9 times more likely to report positive results.	Other (conflicts of interest)	Yes	Yes
Moser et al. (2005)	Schizophrenic patients (*n* =10)	Participants in medication-free schizophrenia research do not show major decline in decisional capacity.	Informed consent	Related terms	Yes
Macias et al. (2005)	Patients diagnosed with schizophrenia spectrum disorder, major depression, or bipolar disorder (*n* = 310)	Match to service assignment preference was a significant positive predictor of service engagements and mismatch was a significant negative predictor of negative engagement.	Value; scientific validity	Related terms	No
Storosum et al. (2005)	Placebo-controlled double-blind studies for the treatment of acute manic episodes (*n* = 11)	There is no increased risk for suicide among the placebo arms of studies.	Fair subject selection	Yes	Yes

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Author/Date	Population/Data Source	Conclusion	Ethical Issues	Ethics Keywords	Explicit Ethics Discussion
Jollant et al. (2005)	Patients with a history of violent (n = 32) or nonviolent (n = 37) suicidal behavior and patients suffering from affective disorders with no history of suicidal behavior (n = 25), and healthy comparison subjects (n = 82)	Both groups of suicide attempters scored significantly lower than healthy comparison subjects on decisional capacity, and violent suicide attempters performed significantly worse than affective comparison subjects.	Informed consent	No	No

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TABLE 3

Hidden Empirical Data on Research Ethics from *Pediatrics* (2005-2006).

Author/Date	Population/Data Source	Conclusion	Ethical Issues	Ethics Keywords	Explicit Ethics Discussion
Lee et al. (2006)	Clinicians who performed procedures on children at an academic tertiary care pediatric hospital (*n* = 35)	Overall, clinicians lack a robust knowledge of assent. Sixty-six percent of clinicians had heard the term, and 35% included the element of seeking the child's agreement as a goal of assent.	Informed consent	Related terms	Yes
Brody et al. (2006)	Adolescents with asthma and their parents (*n* = 36)	Adolescents were less willing to cede decision-making to their parents than parents anticipated.	Informed consent	Yes	Yes
Brahan & Bauchner (2005)	Articles from several journals for two time periods (*n* = 101)	Reporting of race/ethnicity has increased significantly over time, however reporting of gender and socioeconomic status has not increased.	Scientific validity; fair subject selection	Related terms	No
Brassard, Steensma, Cadieux, & Lands (2006)	Retrospective review of newly arrived immigrant children in selected schools (*n* = 2,524)	Twenty-one percent of children tested were positive for a TB skin test, and of those, 92% demonstrated adequate adherence to medication.	Justice; fair subject selection	Related terms	No
Parkes et al. (2006)	Children with a diagnosis of ambulant, early impairment cerebral palsy (*n* = 487)	Case registers have a valuable contribution to make to clinical research by providing a sampling frame, including information on baseline characteristics of an affected population.	Fair subject selection	Related terms	No
Iltis, DeVader, & Matsuo (2006)	Surveys of authors conducting and publishing pediatric research (*n* = 81)	Payment practices and the reasons for adopting certain payment practices varied. Only half of institutions have a pediatric payment policy.	Favorable risk/benefit ratio	Yes	Yes
Kimberly et al. (2006)	IRB-approved informed permission- assent consent forms (*n* = 69)	Compensation and procedures for obtaining child assent & informed permission ranged widely within and across studies.	Informed consent	Yes	Yes
Meyer et al. (2006)	Parents whose children had died in PICUs after withdrawal of life support (*n* = 56)	Parents identified six priorities for pediatric end-of-life care.	Favorable risk-benefit ratio	Related terms	No
Anttila et al. (2006)	Randomized controlled trials on efficacy of physiotherapy interventions on children with cerebral palsy (*n* = 15)	Inadequate reporting methods for many items, measured by CONSORT reporting standards.	Scientific validity	Related terms	No

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Author/Date	Population/Data Source	Conclusion	Ethical Issues	Ethics Keywords	Explicit Ethics Discussion