

ORIGINAL RESEARCH

The Effectiveness of an Educational Brochure as a Risk Minimization Activity to Communicate Important Rare Adverse Events to Health-Care Professionals

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ABSTRACT

Introduction: Educational brochures are an important tool for communicating risk to health-care professionals. It is important to evaluate the impact of any risk minimization tool to understand the effectiveness of the strategy. The objective of this study was to assess the effectiveness (i.e., respondents' awareness and understanding of the communication) of a targeted educational brochure distributed to health-care professionals (HCPs) as a risk minimization strategy for the communication of new rare and important adverse events (AEs).

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Methods: A prospective, non-interventional, online survey was performed following distribution of a specifically designed brochure highlighting new and important adverse events to a targeted HCP population, consisting of known users of the target medicine, as represented by a commercial database. Predefined multiple-choice survey questions assessed overall HCP awareness of the brochure and understanding and retention of information in those HCPs who reported receiving the brochure.

Results: The educational brochure was sent to a total of 565 HCPs; 121 (21.4%) responded to the survey. The majority of respondents (95.0%) had previously prescribed or dispensed the target medicine. In all, 88 (72.7%) respondents said they had received the educational brochure, of whom 95.5% stated they had at least scanned the main points. More participants who had received the brochure (86.4% to 96.6%) answered the five individual survey questions correctly compared with those who did not (51.5% to 97.0%); this was significant for four out of five questions ($P \leq 0.005$). Significantly more HCPs who received the brochure achieved the predefined

pass rate (at least four of five questions answered correctly) compared with HCPs who did not receive the brochure (93.2% vs 57.6%, respectively; $P = 0.000003$).

Conclusions: Distribution of targeted educational brochures may be an effective risk minimization strategy to raise HCP awareness of new rare and important AEs; educational brochures may also be an effective channel for sharing information on how these AEs can be best managed and on the importance and means of reporting AEs.

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INTRODUCTION

Dissemination of important or newly identified clinical safety information to health-care professionals (HCPs) is a key factor in improving patient management and outcomes, and additional risk minimization measures are often required for specific medicines to ensure that the benefits of the products outweigh the risks. However, while it is important to evaluate the impact of any risk minimization tool to understand the effectiveness of the strategy, guidance and methods for evaluating these measures are constantly evolving [1]. The effectiveness of routine risk communication and risk management delivered via the prescribing information for a medicine has been challenged for reasons relating to increasing complexity, poor design and presentation, and a lack of clarity [2]. This may be particularly

relevant to oncology products, where the information about safety is often not only extensive and complex, but vital.

Health-care professionals are exposed to a vast range of information on medicines via traditional printed materials (prescribing information, product monographs, publications in peer-reviewed journals, guidelines) and numerous other sources (educational campaigns and programs, specialist Internet sites, marketing material from pharmaceutical companies). This means that keeping HCPs up to date and fully informed about clinically important new safety information associated with a particular medicine can be challenging. Additional educational tools, like HCP-targeted brochures, may be an effective way of communicating important information to HCPs in specific therapeutic areas. Printed educational materials (delivered by either traditional mail or in an email-friendly digital format) are widely used to disseminate information. Printed materials offer many benefits that make them well suited to the often rapidly changing knowledge base and recommendations for certain types of medicines—they are familiar, accessible, inexpensive, and convenient to use and, as such, have the potential to provide an effective method for disseminating information to HCPs [3]. In addition, printed materials have been shown to have a small beneficial effect on professional practice outcome compared to no intervention [3].

To determine whether such materials could be an effective way of minimizing safety risks associated with an individual medicine, we investigated the impact of the distribution of an educational brochure (supplemental materials: educational brochure) targeting relevant HCPs in Australia; in this case, the brochure was focused on awareness of new rare

and important adverse events (AEs) associated with the use of nanoparticle albumin-bound paclitaxel [nab-paclitaxel; Abraxane®; Specialised Therapeutics Australia Pty Ltd (STA), Kew East, Victoria, Australia]. The educational brochure was distributed on behalf of the sponsor (Abraxis BioScience Australia Pty Ltd, an indirect subsidiary of Celgene Corporation) in response to a request from the Australian Government Department of Health Therapeutics Goods Administration (TGA) to implement an additional risk minimization measure.

In Australia, nab-paclitaxel was first approved by the TGA for the treatment of metastatic carcinoma of the breast following failure to respond to anthracycline therapy, and was more recently approved for non-small cell lung cancer and metastatic adenocarcinoma of the pancreas. Three new rare and important safety concerns (cranial nerve palsies, cardiotoxicity, and Stevens–Johnson syndrome/toxic epidermal necrolysis) were identified from post-marketing surveillance of nab-paclitaxel AE reports, and were subsequently included in the nab-paclitaxel prescribing information and the risk management plan. In line with their increasing focus on the post-approval safety profile of medicines in the clinical setting, the TGA recommended enhanced risk minimization activities for these safety concerns. As part of these activities, the sponsor and the TGA agreed that an educational brochure should be disseminated to specialist oncologists and pharmacists. This brochure was designed to raise HCP awareness of three new rare and important AEs and show how they can be best managed—emphasis was placed on the importance of reporting these events, and on providing information on where to report such events if encountered. To

determine the effectiveness of the educational brochure as a method of additional risk minimization, a survey (supplemental materials: survey) of the HCPs who had been sent the brochure was conducted; questions were constructed to assess coverage, awareness, and transfer and retention of the information provided.

METHODS

Study Design

This was a prospective, non-interventional, cross-sectional study. The TGA was consulted throughout the protocol development process. The HCP brochure distribution and subsequent survey were designed to be deployed to approximately 600 HCPs comprising medical oncologists, oncology pharmacists, and directors of pharmacy as listed in a database maintained by STA. The STA database consists of medical oncologists and oncology pharmacists known to STA through commercial activities and includes all known users of nab-paclitaxel in Australia. As such, the database provided a highly targeted group of HCPs who used, prescribed, and/or dispensed the target medicine.

A two-page HCP brochure entitled “Abraxane: Understanding Rare Important Side Effects” was first prepared and published in Q3, 2012, and initially distributed by sales representatives during face-to-face visits with HCPs. On March 1, 2013, hard copies of the brochure were posted to approximately 574 HCPs in Australia (medical oncologists, oncology pharmacists, and directors of pharmacy). On November 1, 2013, an updated brochure, which included new indications for non-small cell lung cancer and pancreatic

adenocarcinoma, was sent via email exclusively to HCPs newly identified since the March 1, 2013 distribution. The final distribution of this HCP brochure was via email to 574 HCPs on September 24, 2014, together with a link to the Abraxane® product information (current at the time of the survey). As part of the final distribution, the HCPs were informed that the brochure formed part of the risk minimization strategy for nab-paclitaxel and were given advance warning that a survey would be sent in approximately 1 week to assess their understanding of the information provided in the brochure.

Survey Design and Deployment

The survey was an online survey consisting of five initial multiple-choice questions (Part 1) which collected data on the job role and location (state) of the HCPs and their prior experience with nab-paclitaxel, and assessed whether the HCPs had received and read the educational brochure. In Part 2 of the survey, the respondents' recall of facts included in the educational brochure was assessed using five multiple-choice questions concerning: identification of AEs; management and treatment of induced cranial nerve palsies; identification of patients at risk of cardiotoxicities; management and treatment of Stevens–Johnson syndrome/toxic epidermal necrolysis; and AE-reporting procedures if such rare risks were identified.

To encourage the completion of all survey questions, partial completion of the survey or failure to pass (pass defined as correct response to at least four out of five questions answered) on the first attempt resulted in a prompt to repeat the unanswered or incorrectly answered questions.

To minimize bias in responses, the HCPs who were sent the survey had no face-to-face visits or contact with the sponsor's representatives to specifically discuss the HCP brochure or survey; in addition, survey questions were designed to be non-leading. The survey was designed so that it could be completed from any electronic device.

Between September and October 2014, HCPs were sent an email with an invitation to participate in the online survey. The first invitation was sent 1 week after distribution of the HCP brochure, and reminders were sent to non-responders once a week over a 3-week period. HCPs were offered a small monetary incentive to complete the survey. Unique IDs assigned to responders ensured that each respondent could participate only once in the survey.

Study Outcomes

The primary aims of the study were to: (a) monitor and (b) assess the effectiveness of the educational brochure in accordance with the medicine's proposed risk minimization program for Australia. The process used was similar to that outlined by Banerjee et al. [1], and based on the European Medicines Agency (EMA) Good Pharmacovigilance Practices (GVP) Module XVI [4] and the Council for International Organization of Medical Sciences (CIOMS) IX report [5]. The study effectively assessed the first three levels of the Banerjee model using two main process indicators: *awareness*, which measured the coverage and awareness of the educational brochure across the target population of interest; and *understanding/knowledge*, which assessed target respondents' understanding of information contained in the brochure using five predefined multiple-choice questions.

For the purpose of the study, the educational brochure was considered to be a valid method for risk reduction if a predefined $\geq 80\%$ of HCP respondents answered $\geq 80\%$ (four out of five) questions from Part 2 of the survey correctly.

Data Analysis

The data were summarized and analyzed descriptively based on the total number of HCPs who were sent the educational brochure to evaluate the defined process indicators. Awareness was assessed by the number and percentage of HCPs responding to the survey, the number and percentage of HCPs confirming receipt of the educational brochure, and the number and percentage who had confirmed reading the brochure. Understanding/knowledge was assessed by the number and percentage of HCP responders who passed the survey; assessment of pass rate [percentage of HCPs who responded and passed the survey (defined as correctly responded to at least four out of five questions in Part 2 of the survey)]; and number and percentage of HCPs who correctly answered each of the questions in Part 2 of the survey. Results from respondents who had received the brochure were also compared with that from respondents who had not received the brochure (obtained from information collected from Part 1 of the survey).

RESULTS

The final database included 574 HCPs who were sent the educational brochure. Seven HCPs in the database with undeliverable or disabled email addresses and two with out-of-office responses were removed from the study population, giving a final effective sample of 565 HCPs. Of these, 121 (21.4%) responded to the survey. The profile of the respondent sample

is shown in Table 1. Overall, the respondent sample reflected the structure of the original database, only with a slightly higher proportion of oncology pharmacists (Fig. 1). The majority of survey respondents had previously prescribed or dispensed nab-paclitaxel (overall: 95.0%; oncology pharmacists: 95.0%; hemato-oncologists: 100%; medical oncologists: 94.9%).

Awareness

In all, 88 (72.7%) respondents said they had received the educational brochure (Fig. 2). More oncology pharmacists (87.5%) said they had received the brochure than did oncology clinicians (65.4%).

Overall, 70.2% of the total survey participants (i.e., including those who had received and those who had not received) stated they had read the educational brochure. Of those respondents who reported having received the educational brochure, a high proportion stated they had read it (95.5%), with similar findings in oncology pharmacists (97.1%) and oncology clinicians (94.3%). All other respondents who received the educational brochure stated that they intended to read it. Of those recipients who had read the educational brochure, the majority (65.9%) stated that they had scanned the main points, and more than a quarter (29.5%) stated that they had read it in detail (Fig. 2).

Understanding

Overall, 83.5% of all HCPs who responded to the survey answered at least four out of five questions correctly, with similar results in oncology pharmacists (90.0%) and oncology clinicians (80.2%). However, significantly more HCPs who received the brochure answered four

Table 1 Sample profile, n (%)

	Medical oncologists	Hemato-oncologists	Oncology pharmacists	Total
New South Wales	24	1	9	34
Victoria	29	0	13	42
Queensland	13	0	3	16
South Australia	3	0	4	7
Western Australia	5	0	7	12
Tasmania	3	1	4	8
Northern Territory	1	0	0	1
Australian Capital Territory	1	0	0	1
Total	79	2	40	121

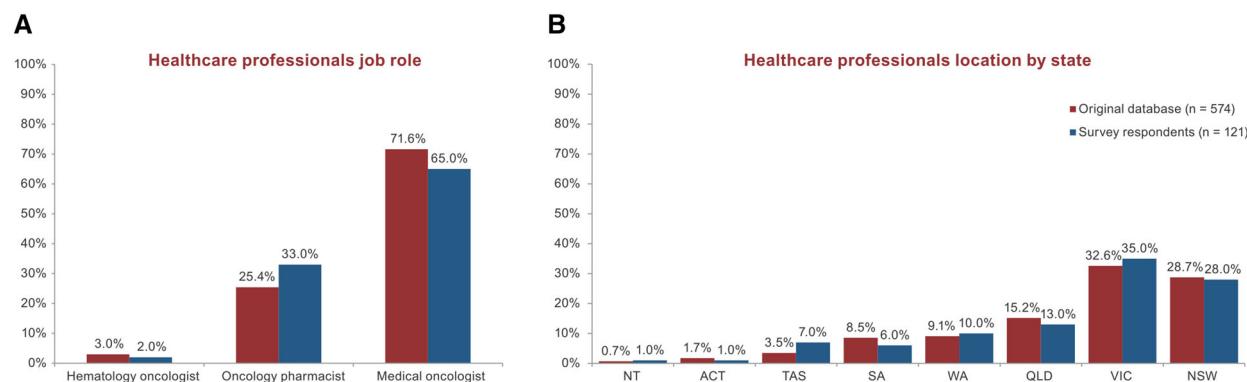


Fig. 1 Survey participant demographics. (a) Job role, (b) location. *ACT* Australian Capital Territory, *NSW* New South Wales, *NT* Northern Territory, *QLD*

Queensland, *SA* South Australia, *TAS* Tasmania, *VIC* Victoria, *WA* Western Australia

or five questions correctly compared with HCPs who did not receive the brochure (93.2% vs 57.6%, respectively; $P = 0.000003$).

In the multiple-choice questions comprising Part 2 of the survey, each of the individual five survey questions, designed to assess the understanding of information in the brochure, was answered correctly by at least 76.0% of the total respondent sample; however, for the majority of questions, the proportion of

respondents answering correctly was significantly higher in those who had received the educational brochure compared with those who did not (Fig. 3).

DISCUSSION

The results of this study provide important insights into the effectiveness of an educational brochure as a post-marketing risk minimization

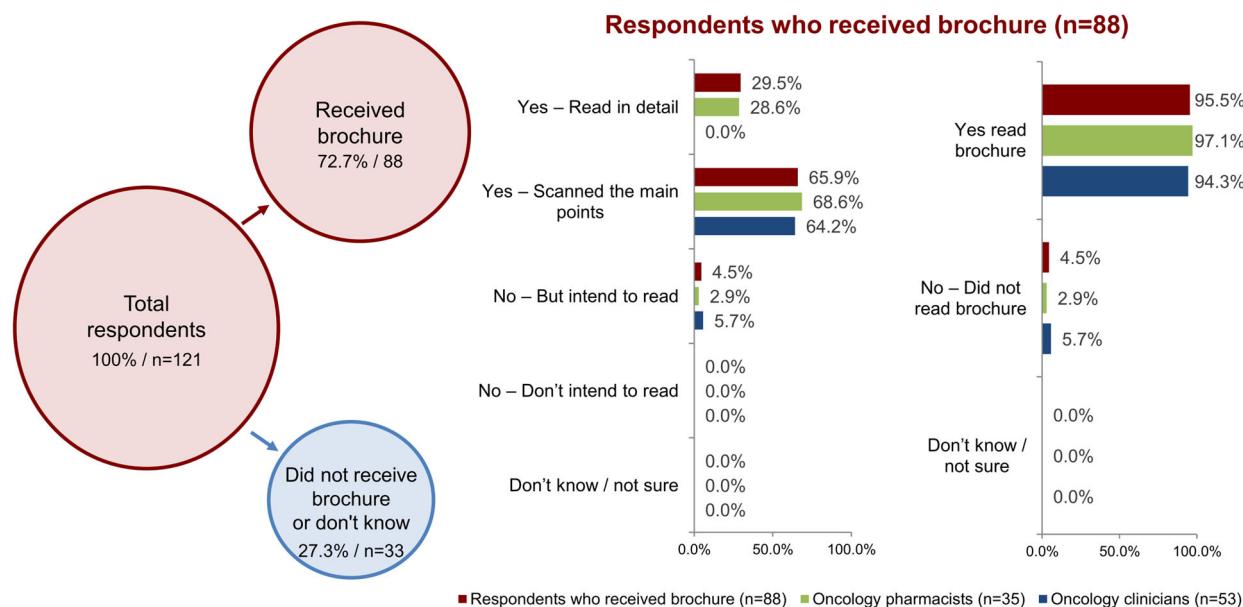


Fig. 2 Respondents' awareness of the communication

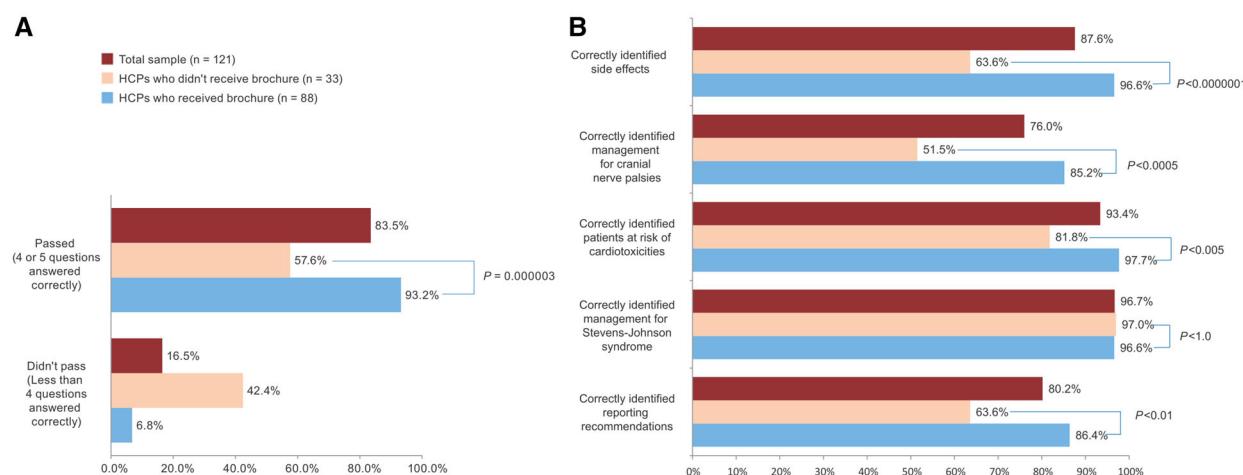


Fig. 3 Proportion of HCPs who answered/understood the survey questions correctly (a) overall, (b) for each question. *HCP* health-care professionals

strategy for the communication of information on new rare and important treatment-associated AEs. Almost three-quarters of those HCPs who responded acknowledged receipt of the educational brochure, and almost all who acknowledged receipt reported that they had read the brochure. This suggests that there is a high

likelihood that for clinicians like those who responded to the survey, this educational brochure will be read—provided it can be successfully distributed to health-care professionals. The efficacy of the educational brochure in raising awareness of new rare and important AEs was demonstrated by the fact that a significantly higher proportion of

responders who received the brochure were able to correctly answer survey questions compared with HCPs who did not receive it, with a significantly higher proportion of responders who had received the brochure attaining the predefined pass rate compared with those who had not received the brochure.

Evaluation of the effectiveness of any drug risk minimization tool is important to understand the effectiveness of the strategy; however, to date, there is only minimal guidance available [4–6]—and even this guidance does not provide detailed methodology for evaluation of risk minimization activities. To our knowledge, this is the first study to successfully measure the effectiveness of an educational brochure in communicating information on new rare and important treatment-associated AEs to HCPs.

The evaluation of the effectiveness of risk minimization interventions is a pivotal part of continuous pharmacovigilance, and an analysis of interventions implemented—and whether they have been successful in reducing risk—is crucial [7]. While proof of risk reduction is pivotal to any risk management strategy [7], it is beyond the scope of this study. However, proof of implementation is an equally important step in risk management strategies and is necessary if we are to assess subsequent data regarding the reduction of risk. Should a particular strategy fail to reduce risk, assessment of implementation will help determine whether this failure arose at the implementation stage, or was the result of a conceptual error in the strategy itself [7].

Pharmaceutical companies primarily communicate risk through labeling tools such as the prescribing information, package insert, patient information leaflet, and the carton [2]. However, the efficacy of such approaches has been poorly investigated, and recent research has raised concerns over the effectiveness of

some of these methods [2]. The evidence behind the effectiveness of printed materials in disseminating information and influencing HCP behavior is inconclusive. A recent Cochrane review looked at a range of studies evaluating the impact of the distribution of printed educational materials on HCP practice and patient outcomes [3]. This analysis included studies using a wide range of distribution techniques including personally addressed communications, communications delivered via mass mailings, and passively delivered communications utilizing broader communication channels (e.g., printable documents available on the Internet, mass media). The conclusion of the study was that printed educational materials, when used alone and compared with no intervention, have a small beneficial effect on professional practice outcomes [3]. The Cochrane analysis included only those studies assessing the impact of published or printed recommendations for clinical care, such as clinical practice guidelines, monographs, health authority guidelines and recommendations, and publications in peer-reviewed journals. While there are a number of studies focusing on the impact of these publications on clinical practice, there are fewer addressing the value of more focused, issue-driven printed educational materials in raising awareness of specific clinical issues. A Canadian study investigating physician knowledge of the AEs of treatment with androgen-deprivation therapy found that a significant proportion (82%) of primary care providers would use educational resources to increase their knowledge of AEs if they were available (52% and 32% preferred continued medical education and educational pamphlets, respectively) [8]. A study investigating the efficacy of a hepatitis C virus education

program in Victoria, Australia, found that HCPs who read a post-program feedback brochure were more likely to correctly identify key issues in hepatitis C risk, prognosis, and management [9]. An Australian study investigating whether the distribution of electronic newsletters, containing case studies and lessons learned on deaths in residential care, could influence HCPs found that around half of the respondents to the survey reported changing their professional practice as a result of reading the communiqués, with around one-fifth agreeing they would not have made the changes if they had not read the publication [10].

Our study has a number of strengths. The survey performed in this study was in line with United States Food and Drug Administration (FDA)-recommended practice for survey methodologies used to assess the effectiveness of risk evaluation and mitigation strategies [6]. Key risk messages were identified, and the questionnaire developed to target these key risk messages. By using the STA database, we were able to target relevant HCPs (i.e., those who used, prescribed, and/or dispensed the target medicine) and provide a representative sample of the entire population of product users. This along with avoidance of the use of leading questions limited bias. The short length of the survey, which was easy to complete using any electronic device, minimized the burden imposed on the survey participants. Shorter and simpler documents have the potential to facilitate more effective and efficient uptake of key information, given that HCPs may not have time to screen and appraise new scientific literature [3], or to read longer formal documents such as full prescribing information in detail.

In addition, by asking the question “Did you read the brochure: Yes or No?” we were able to

provide a comparator group which is often lacking in studies of this type. This was a prospective study with a predefined measure of success (pass rate). Finally, we consulted with and received input from the regulator in the design of the study and outcomes.

There are limitations inherent to the nature of this study which should be considered. In common with many other survey-based studies, responder bias (only around one-fifth of HCPs responded to the survey) may have influenced the results of the current study, and the results may not be generalizable to a wider population or to other clinical areas. HCPs, particularly clinicians, generally show a low rate of response to surveys—and the rate of response has declined over recent decades [11–13]. However, and despite these limitations, surveys are an efficient, inexpensive, and flexible means of collecting information from a large pool of respondents and an important means of assessing and evaluating information dissemination [12, 13]. For the current study, the results of the survey were accepted by the TGA to demonstrate the effectiveness of the educational brochure as an enhanced risk minimization activity for nab-paclitaxel, and it was agreed that repeat distribution of the educational brochure was not necessary.

CONCLUSIONS

Our study suggests that targeted educational brochures are a useful communication mechanism for clinicians like those who responded to the survey to raise HCP awareness of new rare and important AEs; they are also effective in sharing information on how these AEs can be best managed and on the importance and means of reporting AEs. Such brochures may be of particular use as part of risk

minimization strategies in rapidly changing fields such as oncology, where HCPs need to deal with increasing complex medicines and protocols to treat cancers.

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Disclosures. Nicolette Bester is an employee of Specialised Therapeutics Australia Pty Ltd. Michelle Di Vito-Smith, Theresa McGarry, and Michael Riffkin are employees of Celgene Pty Ltd. Stefan Kaehler is an employee of Celgene Europe Ltd. Richard Pilot and Robert Bwire are employees of Celgene Corporation.

Compliance with Ethics Guidelines. This non-interventional risk minimization activity does not require the agreement from an independent ethics committee since it does not involve the use of subjects.

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