Variability in IRBs Regarding Parental Acceptance of Passive Consent

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ABBREVIATIONS
HIPAA—Health Insurance Portability and Accountability Act
IRB—institutional review board
PALISI—Pediatric Acute Lung Injury and Sepsis Investigators
PHI—protected health information

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As institutional review boards (IRBs) evaluate subject recruitment strategies for pediatric clinical research, they must consider all relevant regulations from multiple federal agencies. Despite guidance documents, experts acknowledge that federal regulations remain ambiguous and are inconsistently applied.\textsuperscript{1–4} Multiple studies have demonstrated IRB variability in application of both the Code of Federal Regulations and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.\textsuperscript{5–10} HIPAA requires authorization from patients for use of protected health information (PHI) for research but describes circumstances under which this requirement can be waived for “activities preparatory to research.”\textsuperscript{11} This waiver allows researchers to use PHI to identify and contact potential participants for recruitment purposes.\textsuperscript{11,12} Passive consent, commonly termed opt-out consent, assumes agreement to study participation unless consent is deliberately withdrawn. In one form of passive consent strategy, study information is presented to a pool of potential study participants in the form of a letter. Withdrawal of consent (opt-out) by telephone call or return postage is required for removal from the pool. Passive consent is widely used in research conducted in the outpatient setting, social sciences, and other disciplines\textsuperscript{13,14} but has rarely been used in pediatric clinical studies; it is not universally accepted by IRBs.

In collaboration with the Centers for Disease Control and Prevention, we developed a multicenter study to evaluate influenza vaccine effectiveness in preventing laboratory-confirmed influenza infection associated with admission to a PICU among children aged 6 months to 17 years. Study centers were recruited through the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, with the study administered through a contractor, Abt Associates Inc ("Abt"), and its survey subsidiary, Abt SRBI. PALISI is composed of primarily academic, pediatric-dedicated hospitals with strong research programs. Each participating center’s local IRB was experienced in reviewing pediatric studies. This case-control study coupled each influenza-positive PICU case with 2 age-matched and influenza severity risk–matched control subjects from the same geographic area. Potential control subjects were identified primarily from general and subspecialty pediatric clinics associated with participating children’s hospitals.

This article details the passive consent strategy for identifying community control subjects as it was approved, modified, and used in this study. We also evaluate modified active strategies used by a subset of pediatric study centers as required by local IRB and the parental response to the passive consent strategy.

**METHODS**

Data were prospectively collected on the strategies used to obtain consent from parents of control subjects in this multicenter pediatric study conducted from September 2009 to July 2011. We then compared opt-out and refusal rates of the passive, opt-out recruitment approach initially approved by the Abt IRB versus the active strategies developed to comply with individual centers’ IRB requirements.

The H1N1 influenza pandemic was expected to continue through the 2010–2011 influenza season with projected high enrollment, and the study design required a large pool of immediately available pediatric control subjects to be matched with enrolled cases. The study was divided into 2 phases: the pre-enrollment phase, designed to generate a pool of potential control subjects and to obtain consent for minimal PHI to be transmitted to Abt SRBI; and the enrollment phase, consisting of parent interviews and consent for their children to participate as study control subjects. Centers using the passive approach identified potential control subjects from children seen in the previous 24 months on-site or in affiliated emergency departments or clinics, with a target of 210 potential control subjects per center. In the pre-enrollment phase, medical records were screened to assign children to age and influenza risk severity tiers for matching with future cases (step 1) (Fig 1). Before enrollment of the first case, an opt-out letter was sent to the parents or guardians of each potential control subject (step 2). This letter detailed the study and provided an

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**FIGURE 1** Passive opt-out strategy for identifying and enrolling matched community control subjects. ED, emergency department.
opportunity for parents to opt out from being contacted by Abt SRBI for consent and study enrollment. Centers removed patient data from control lists if they received an undeliverable letter or an opt-out request before the deadline specified in the letter (step 3). Limited demographic and contact information for the remaining potential control subjects (including the child’s name, birth date, influenza risk severity tier, and parent/guardian name, address, and telephone number) was then securely transmitted to Abt SRBI (step 4). If opt-out requests or undeliverable letters were received after the formal opt-out period and after control contact information had been shared, Abt SRBI immediately destroyed all data for those parents and children.

With each case enrollment, parents or guardians at age- and risk-matched control households were called by representatives from Abt SRBI. In the early enrollment phase (step 5), interviewers used an IRB-approved screening script to confirm age, influenza risk severity tier, and address to verify eligibility for enrollment as a study control subject. Once eligibility was verified and verbal consent obtained, Abt SRBI staff completed the telephone interview (step 6). If verbal consent was not obtained, the interview was terminated, and no further participation occurred. For participants who completed the interview, formal written consent documents were mailed to obtain signed consent and HIPAA authorization for study personnel to acquire records to verify parent-reported underlying conditions and vaccination status (step 7). Once the signed consent was received, vaccination records were obtained from the child’s provider (step 8), and the study center securely transmitted detailed clinical information to Abt (step 9). Abt collected data regarding the number of potential control subjects contacted, completed surveys, and refusals. Principal investigators or research coordinators at each participating center confirmed final community control recruitment numbers by study closeout survey; these data were separately verified for this study.

The primary outcome for the present study was to describe IRB variability at children’s hospitals in acceptance of the study’s proposed passive consent strategy for generation of a pool of potential study participants. In addition, we provide descriptions of approved active recruitment strategies used in a subset of centers where IRBs did not approve the passive consent strategy. Secondary outcomes include the effects of the passive consent strategy by comparing opt-out and refusal rates during the pre-enrollment and enrollment phases between active and passive strategy groups. The opt-out rate in the passive consent group was calculated by dividing the total number of opt-out requests received by the number of letters sent minus letters returned as undeliverable. The declination rate in the active consent group was calculated by dividing the total number of declined consents by the attempted requests minus failed contacts. Refusal rates were calculated by dividing the number of potential participants who refused to participate in the telephone interview or refused to allow their child to participate as a control by the number of households contacted (numbers dialed minus failed contact attempts).

Statistical analysis was completed by using GraphPad (GraphPad Software, Inc, San Diego, CA; 2013). A 2-tailed Fisher’s exact test was used to compare differences between groups. P values < .05 were considered statistically significant.

RESULTS

Twenty-six pediatric centers completed IRB submissions for this study; 24 participated. Two centers did not participate due to inability to staff the project to meet IRB requirements for active consent. Sixteen centers received local IRB approval to use the passive approach for recruitment of control subjects as previously described. Six local IRBs required active strategies; 2 centers participated as ICU enrollment-only centers, using matched control subjects provided by another participating center in their region (Fig 2). Although not quantified in our data, most study centers reported following their usual practice of notifying clinic or specialty pediatricians of intent to recruit children from clinic records. The practice of advance physician notification is reported as a professional courtesy but is not a formal IRB requirement.

The 6 centers required by their respective IRBs to develop an active control recruitment strategy worked with the Centers for Disease Control and Prevention, Abt, and the primary study investigators to design the methods. All the centers used an advance parental

FIGURE 2
IRB submissions and approvals.
consent strategy, in which the research team contacted parents of potential control subjects in person or by telephone to obtain verbal and/or written consent to release minimal PHI to Abt SRBI (before step 4 in Fig 1) for placement into the pool of potential control subjects. Local IRBs required scripts for in-person verbal consent. Each of these 6 centers used medical record screening to identify potential control subjects before contacting them. Three centers prescreened medical records of children with upcoming outpatient visits for age and influenza risk severity tier stratification. The research team approached these families in waiting areas about study participation and obtained written consent to provide minimal PHI to Abt SRBI (before step 4 in Fig 1) for placement into the pool of potential control subjects. Local IRBs required scripts for in-person verbal consent. Each of these 6 centers used medical record screening to identify potential control subjects before contacting them. Three centers prescreened medical records of children with upcoming outpatient visits for age and influenza risk severity tier stratification. The research team approached these families in waiting areas about study participation and obtained written consent to provide minimal PHI to Abt SRBI.

The final 2 centers prescreened potential community control subjects in the same manner as in the passive strategy but securely retained the data on-site. When a case subject was identified, potential control subjects were randomly selected and matched to the case subject by using age and influenza risk severity tier. The center research team called these families to obtain verbal consent to release minimal PHI to Abt SRBI, who then contacted them for potential study enrollment. This information was transmitted only after the local investigators obtained verbal consent.

**Enrollment Summary**

A total of 4529 children were identified as potential control subjects across 22 centers. From the pool of potential controls, 452 telephone numbers were dialed and 217 potential controls contacted: 41 in the active consent group and 176 in the passive consent group. In the pre-enrollment phase, declination rates were significantly higher in the active recruitment centers compared with opt-out rates in the passive recruitment centers (active: 11.8%; passive: 1.6% [P < .001]) (Fig 3). However, during the enrollment phase, the parental refusal rate at passive recruitment centers was significantly higher compared with active centers (38.1% vs 12.2%; P = .004). Our refusal rate combined across both groups was 33.3%. No participating centers’ IRBs or principal investigators received any complaints from parents or providers regarding any of the recruitment strategies.

**DISCUSSION**

To our knowledge, this is the first pediatric study to demonstrate the inconsistency among IRBs at large pediatric hospitals regarding the application of federal regulations pertaining to passive recruitment and consent processes. This inconsistency may decrease the validity of multicenter pediatric studies, both through added interinstitution variability and by introducing sampling bias. The added cost and labor burden required by active consent strategies also decreased the feasibility of participation at some research centers. Although pre-enrollment refusal rates were higher for centers using active consent strategies, once this study progressed past pre-enrollment to the enrollment phase, parents of children placed into the control pool via the passive approach were more likely to refuse participation than those recruited by the active strategies. In either strategy, parents had the opportunity during both the pre-enrollment and enrollment phases to refuse participation. Despite higher refusal rates during the enrollment phase of the passive strategy, no complaints were received regarding the recruitment and consent procedures, suggesting parent and provider acceptance of the opt-out strategy. It is unclear whether active strategies afforded any added subject protection to justify the markedly increased research staff resources needed to use them.

Literature review demonstrates that passive consent strategies improve recruitment compared with active consent strategies. Our study has a refusal rate similar to those in previously published studies using passive consent and a response rate similar to those reported in general survey research. The opt-out strategy was used in this study to develop a large pool of control subjects from an unbiased sample of participants in anticipation of rapid enrollment during a pandemic and to reduce selection bias over other recruitment strategies. A key feature of active strategies is reliance on investigator recruitment
rather than voluntary participation as in response to flyers, posters, or mailings, methods that are known to introduce voluntary selection bias.\textsuperscript{18,21} As much as possible, the active approaches in this study were designed to reduce the selection bias associated with voluntary participation; active strategies still carried risk of selection bias, however, in that they typically targeted smaller populations than passive strategies. Sites that approached potential subjects based on scheduled clinic appointments effectively generated a convenience sample, which is known to be less representative.\textsuperscript{21,22} Two centers required control subjects collected at other pediatric centers within the same geographic region, introducing other potential bias into the study. Clearly, study validity would have been enhanced by consistent methods across all centers.

Passive consent provides a method to recruit an unbiased pool of potential research subjects from a large representative population\textsuperscript{17}; however, IRB variability may limit the usefulness of this strategy in multicenter pediatric studies, as has been demonstrated in adult literature.\textsuperscript{5,7,8,17} Although our passive consent design for community control recruitment incorporated specific allowances permitted by federal regulations,\textsuperscript{3,6} it was still unacceptable to 10 of 26 IRBs. The passive recruitment process was used in this study to generate a control pool, which meets guidelines for “activities preparatory to research” and is allowable under the HIPAA Privacy Rule with a partial waiver of consent.\textsuperscript{12} The partial waiver allows covered entities to use and disclose PHI to researchers to aid in study recruitment. It is not considered a waiver of consent pertaining to participation in research as defined in federal human subjects regulations, because specific consent forms were mailed and signed before detailed medical information was released to Abt SRBI. However, some IRBs requiring active recruitment strategies specifically cited concerns that waiver of consent/HIPAA authorization was not requested and/or was not appropriate for this study. Similar to published findings,\textsuperscript{6,8} other IRBs in our study felt that it was inappropriate to release any personal contact information without active consent, even though the passive consent strategy met HIPAA allowances. Although IRBs have always been able to make decisions that are more conservative than the minimum standards established by the federal regulations, these findings demonstrate that institutions have a varied interpretation of the criteria for waiving
HIPAA authorization for activities preparatory to research. HIPAA stipulations also exist for contracting with business associates (contractors and subcontractors that receive/use PHI) to assist in contacting individuals. Abt and the centers used a detailed data protection plan, which met all HIPAA standards. At least one IRB requiring active methods cited specific concerns regarding Abt’s assumption of liability for protection of participants’ health information. Three IRBs required a business associate agreement before approval of passive methods. The proposed 2013 update to the HIPAA Privacy Rule, which includes extending requirements to business associates, may address some of the hesitancy of institutions to waive authorization for recruitment purposes.

It is unclear whether active strategies better protected the rights and welfare of children and parents in this study; however, they required substantial clinician effort and resources. Although we were successful in accommodating IRB requirements in 22 (85%) of 26 potential centers, 2 centers did not enroll local control subjects and 2 additional centers were unable to participate in the study because of the burdens of active recruitment. The need for revision and resubmission of protocols restricts the ability of potential study sites to participate because it increases time to approval and staff hours used. Because it was impossible to predict what population of children would be most affected by influenza, it was necessary for the larger study that a robust pool of potential control subjects exist with a diverse sample of age and risk tier controls. Given the lower than expected enrollment of cases, active recruitment strategies for control subjects were manageable for these 6 centers but might not have been feasible if case enrollment numbers had met projections.

Our study presents notable limitations. Lower than anticipated case enrollment precluded an extensive survey of our control pool, and this outcome may have skewed refusal rates. We did not collect parental reasons for opting out, which might have elucidated key details about parental opinions of passive enrollment. We also have no data on time to IRB approval, number of revisions or resubmissions required, or type of revisions, other than consent strategy stipulated by local IRBs. These data would have allowed further comment on variation in IRB assessment of risks and benefits, in the overall study as well as specific to the recruitment strategy.

CONCLUSIONS

The variability in IRB interpretation of regulations regarding passive consent for recruitment introduced potentially unnecessary bias into selection of the control pool for this large pediatric multicenter study. Parental acceptance of a passive consent opt-out strategy was overall acceptable, with no complaints in the pre-enrollment phase. As would be expected, parents declined participation in the active enrollment phase at higher rates than if actively approached pre-enrollment. Because not all potential control subjects in a pool will be matched to an enrolled case subject, use of a passive consent process markedly decreased the research staff workload at the participating sites compared with an active approach strategy. We believe that IRBs should have a consistent approach to evaluating studies requesting opt-out passive consent. Our study supports the use of opt-out consent when identifying potential community control subjects and demonstrates the need for additional guidance on HIPAA regulations pertaining to passive consent options for recruitment.

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REFERENCES


23. Modifications to the HIPAA Privacy, Security, Enforcement, and Breach Notification rules under the Health Information Technology for Economic and Clinical Health Act and the Genetic Information Nondiscrimination Act; other modifications to the HIPAA rules. *Fed Regist.* 2013;78(17):5565–5702
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