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Human Subjects Protection: An Event Monitoring Committee for Research Studies of Girls from Breast Cancer Families

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Abstract

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Purpose—Researchers must monitor the safety of research participants, particularly in studies involving children and adolescents. Yet, there is limited guidance for the development and implementation of oversight committees for psychosocial, behavioral intervention and observational studies.

Methods—We implemented a model for an Event Monitoring Committee (EMC) in three related studies recruiting 6–19 year old girls from families with and without breast cancer.

Results—The EMC model can be valuable for investigators and local IRBs when additional oversight is desired. Recommendations are provided and intended to be broadly applicable to a wide range of research activities designed to improve the health of children, adolescents, and families. EMC goals, membership and procedures for monitoring and assessing risks and benefits should be defined, but should also be flexible and tailored to the study design and population. The EMC model also provides an independent comprehensive, study-wide oversight mechanism for multi-center psychosocial, behavioral intervention and observational studies.

Conclusions—An Event Monitoring Committee provides an alternative oversight approach where additional independent assessment and oversight of study related risks is desired, particularly in the setting of vulnerable populations, children and adolescents, or where risks non-traditional to the medical field (i.e. social, emotional or cultural) are possible.

Keywords

Children and Adolescents; Human subject protections; Research ethics; Data safety monitoring; Event monitoring committee

Monitoring the safety of participants in clinical trials and minimizing associated risks is essential to safeguarding human subjects and to the ethical conduct of clinical research (1). This is especially true for vulnerable populations including minors. One of the more complex and ambiguous issues in research ethics is classifying and quantifying psychosocial risks of participation in research among minors, especially with regards to participation in psychosocial research including behavioral interventions and observational and descriptive studies. Such research does not typically require the oversight of medical clinical trials, but has the potential to significantly impact stress and behavioral outcomes (2–4) among participants. While the benefits of such research typically are thought to outweigh the risks, youth may be especially vulnerable to potential risks given their limited exposure to research and/or the subject matter of the research, which may be unpleasant (e.g., focus on negative events or emotions) immature coping and cognitive skills, and susceptibility to influence. Thus, approaches to monitor risks in studies with minors with the potential to cause distress or negative behaviors are needed.

The Common Rule provides the legislative framework and specific requirements for review, approval, and oversight of any human subjects research supported, executed, and otherwise regulated by the United States (U.S.) government, with additional stipulations in place for select vulnerable populations, including studies involving children and adolescents (5). The Principal Investigator (PI) of a study is responsible for monitoring research risks. Additionally, the National Institutes of Health requires a Data and Safety Monitoring Board (DSMB) for all multi-site clinical intervention trials (6). The NIH also suggests that

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independent oversight may be indicated for Phase I or II trials, psychosocial, behavioral intervention and observational studies, particularly if vulnerable subjects, e.g., minors, are included or there are other significant risks to study participants (2–4, 6–8). Yet, there is limited guidance for the development and implementation of monitoring plans and oversight committees for psychosocial research (3, 4, 8). Several research groups have reported that the traditional DSMB model is inadequate or impractical in psychosocial, behavioral intervention and observational studies (2–4, 9). For example, in the Resources for Enhancing Alzheimer's Care Health (REACH II) study), Czaja et al were required to utilize a DSMB by their sponsoring agencies and reported several challenges to applying a traditional DSMB approach and guidelines to their social/behavioral intervention (4). These included defining adverse events, assigning attributes and defining resolutions, evaluating interim data and addressing baseline events and those detected in the course of the study but not related to study interventions (4).

A potential model for independent oversight in clinical studies that are not required by NIH to utilize a traditional DSMB is an Event Monitoring Committee (EMC) (10). Erwin and Hersch, investigators of two large prospective, observational studies of Huntington's disease, the Huntington's Study Group (HSG), reported the development of, and experience with an EMC, providing a framework for other research teams (10). The HSG noted their EMC model could be valuable in observational studies involving genetically at-risk or vulnerable populations, for whom potential risks might not be physical, but rather emotional, social or economic, or where unanticipated risks might develop (10). To our knowledge, the EMC approach to independent oversight in psychosocial, behavioral intervention and observational studies, has not been described in children and adolescents.

We utilized the HSG EMC model and recommendations provided by Czaja et al. (4) to develop EMCs to monitor potential risks to participants in three observational studies recruiting girls ages 6 to 19 years from families with and without a family history of breast cancer. In this paper, we describe the process of creating and implementing an EMC and provide recommendations for investigators seeking an alternative model for independent oversight of psychosocial, behavioral intervention and observational studies, particularly those involving children and adolescents and those were a traditional DSMB is not easily adapted (4).

METHODS

Overview of the SOFTI and II (Study of Female Teens) studies and the LEGACY (Lessons in Epidemiology and Genetics of Adult Cancer from Youth) Girls Study

Aside from skin cancer, breast cancer is the most common cancer among women in the United States (11). Although genetic testing and screening for breast cancer are not recommended for children and adolescents, early-life events (e.g., exposures, biologic changes) might modify risks for breast cancer in adulthood (12–15) and many health and risk behaviors begin in, or become established during adolescence (16–20). The majority of offspring in high-risk families learn of familial and genetic risks for breast cancer during childhood and adolescence (21–24). Little is known, however, about adolescent girls' knowledge, attitudes and beliefs about breast cancer risks. For example, we do not know

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how adolescent girls think about preventive health and risk behaviors or how their thoughts and behaviors change throughout psychological and physical development. To address this critical knowledge gap, we conducted the "Studies of Female Teens" (SOFT I and SOFT II studies) and included a psychosocial/behavioral component in the "Lessons in Epidemiology and Genetics of Adult Cancer from Youth" (LEGACY) Girls Study to evaluate knowledge and perceptions of breast cancer risk and health behaviors in girls 6 to 19 years of age from families with and without breast cancer. The objectives and methods of these studies are summarized in Table 1.

Rationale for an Event Monitoring Committee for the SOFT and LEGACY Girls studies

Several features and contextual aspects motivated us to incorporate an EMC for the SOFT and LEGACY Girls studies. First, the studies recruit children and adolescents, who require additional protections (5). Second, while there are some studies evaluating psychosocial outcomes in daughters of breast cancer patients and survivors of childhood cancer (25–28), there are limited available data and experience interviewing adolescent girls at familial or genetic risk for breast cancer. Third, we acknowledged that some of our novel questions evaluating knowledge and perceptions of risk for cancer or collection of biospecimens and anthropometric measurements in the LEGACY Girls study might have the potential to be associated with distress or concern among children and adolescent girls, particularly from breast cancer families. Equally important, local Institutional Review Boards (IRBs) expressed similar concerns regarding the vulnerability of the population and the potential for distress. While it might have been appropriate for data and safety monitoring to be conducted solely by the PIs and research team, an EMC could provide valuable input, added oversight and protections to a potentially vulnerable population, and an acceptable response to concerns raised by local IRBs. The EMC oversight plan was included in all study protocols and approved by all site IRBs.

RESULTS

Implementation of an EMC for SOFT I

Similar to the REACH II (4) and HSG EMC model (10), we sought EMC members with multi-disciplinary expertise relevant to the study focus and population. This included members with expertise in General Pediatrics, Research Ethics, Child Clinical Health Psychology, Cancer Genetics, and community members from breast cancer families (i.e., an 18 year-old daughter of a mother with breast cancer and a mother with breast cancer who has a teen daughter). The goals of the EMC were: 1) to analyze and categorize anticipated and unanticipated adverse events (e.g., breaches of confidentiality or psychological distress); 2) to advise investigators on the occurrence and significance of such events; and 3) to recommend approaches to minimize study-related risks.

To achieve these goals, the EMC reviewed procedures to monitor potential study-related events, including providing referrals and resources if any distress or concerns were identified in interviews. For example, the SOFT I EMC reviewed de-identified telephone survey responses for the first 4 participants, with a particular focus on items evaluating perceived risk for cancer, which the IRB identified to be potentially distressing for

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adolescent girls. EMC members had the opportunity to ask research staff conducting interviews about their perceptions of participant willingness and comfort answering survey questions. The research team and EMC identified the potential for girls to disclose sensitive information, including risky health behaviors and/or underlying health issues, particularly in semi-structured telephone interviews. These types of disclosures were not considered "study-related events," but were recognized to be incidental findings that could be important for the health and safety of participants. The EMC reviewed the process the investigators had developed for research staff training and procedures for contacting the PI and Co-I (a Clinical Psychologist) if they had concerns regarding the significance of any unanticipated disclosures by participants. There were no significant adverse events during SOFT I. The EMC supported the research teams' plans to develop quantitative surveys and continued research in mothers and their daughters ages 11–19 years in SOFT II and the LEGACY Girls Study.

Implementation of the EMC for SOFT II and the LEGACY Girls Study

The SOFT II and the LEGACY Girls Study share several features but also have some key differences (Table 1). They both involve parallel quantitative self-administered surveys in mothers and daughters. Importantly, participants in the SOFT II Study completed surveys on-line in their homes and research team members were not able to assess participant responses in real time. In the LEGACY Girls Study, usually daughters completed the baseline behavioral surveys with the study teams in clinic or home visits, although in the longitudinal follow-up girls were allowed to complete the behavioral surveys on-line. Similar to the SOFT I EMC, the EMC membership included 5 multidisciplinary members for SOFT II and the LEGACY Girls Study. For SOFT II, this included members with expertise in general Pediatrics, research ethics, child clinical health psychology, cancer genetics, and community members as in SOFT I. In the LEGACY Girls Study, a five-center study in the US and Canada, the 5 members were selected to ensure regional representation. Given the larger scope of the study aims in the LEGACY Girls Study (see Table x), EMC members were selected to adequately represent the all study aims and included members with expertise in general pediatrics, research ethics, epidemiology, cancer genetics and child clinical health psychology. The decision about incorporating community members versus health professionals was based on preferences regarding the size of the committee, competing membership priorities (ie, representing regional differences, having an odd number for voting purposes, barriers to scheduling with large committees) and EMC Chair preferences and experiences in leading other oversight committees. Like SOFT I, the SOFT II and the LEGACY Girls Study EMCs reviewed study procedures, survey content, and proposed plans to monitor events.

Events in SOFT II and the LEGACY Girls Study could include study-related events (e.g., breach of confidentiality, distress related to study surveys or procedures in the LEGACY Girls Study) or incidental findings (e.g., distress, depression, bullying) unrelated to the study but identified by study questionnaires. These incidental findings are detected by quantitative items that were sensitive, but not sufficiently specific, to identify the type and timing of events or safety. For example, in both studies, mothers and daughters completed items from the Behavior Assessment System for Children II (BASC-2) (29), a validated measure

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assessing daughters' psychosocial adjustment. Items that could indicate potential harm to participants or others were selected by the investigators for review by research staff (e.g., "sometimes I want to hurt myself", someone wants to hurt me") within 72 hours of survey completion. When mothers or daughters responded affirmatively (e.g., sometimes, often, or almost always true), follow-up in-person (at the time of survey completion in a clinic or home visit of the LEGACY Girls Study) or by phone (LEGACY Girls Study and SOFT II) was completed to probe mother and daughter responses and to evaluate the potential for imminent risk to the mother, the daughter, or others. Research staff for both SOFT II and the LEGACY Girls Study underwent training in utilizing standardized protocols developed by adult and child clinical psychologists (Co-Investigators, Patrick-Miller and Schwartz) to evaluate and report perceived risks.

Additionally, all sites in the LEGACY Girls Study developed site-specific and regionally compliant plans to provide referrals in the event harm to participants or others. The EMCs critically reviewed and provided recommendations on these monitoring and response plans. Again, all information shared with the EMC was de-identified. In both studies, participant responses were recorded in an event log with a description of follow-up calls and outcomes, which were provided to the EMC for review. At the time of the initial SOFT II EMC review (and prior to recruitment for the LEGACY Girls Study), 28% of daughters and 11% of mothers responded affirmatively to at least one of the selected BASC monitored items requiring telephone follow-up. The SOFT II EMC review found that none of the positive responses to the selected BASC items had identified any imminent harm. Instead, responses from daughters and mothers suggested that the follow-up calls were perceived as intrusive and unnecessary in most circumstances. As a result, the research team developed follow-up questions embedded in the on-line survey. Triggered by positive responses to the selected questions, the on-line follow-up questions distinguished responses that needed follow-up calls to daughters from those that did not (i.e., past events with no concerns for imminent harm), in order to restrict calls to scenarios where follow-up was needed to clarify any potential for risk and minimize intrusiveness. The EMC played a key role in reviewing these modifications and procedures in the SOFT II Study. This modified monitoring approach was adopted in the LEGACY Girls Study, with review by the LEGACY Girls Study EMC and each of the independent LEGACY Girls Study sites' IRBs.

In both the SOFT II and the LEGACY Girls Study there were no adverse events directly related to study procedures (e.g., distress induced by participation), and there were no incidental findings of imminent harm. For all three studies, the EMCs supported continued recruitment and monitoring of risks of participation, providing key feedback and review throughout each study. While EMC members, coming from a range of disciplines provided varied perspectives, they did not differ significantly in their assessment of the risks, benefits or monitoring procedures of human subjects (e.g. consensus was generally achieved through EMC meeting and teleconference deliberations).

DISCUSSION

Our experience implementing an EMC in three child and adolescent behavioral observational studies suggests that the EMC model can be valuable both for the investigative

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team and the local IRB, when additional oversight is desired. Based on our experiences, we provide several recommendations for implementing an EMC for psychosocial, behavioral intervention and observational studies (Table 2).

Recommendation 1: Consider the value of an EMC in psychosocial, behavioral intervention and observational studies when there is the potential for psychosocial risks or vulnerable populations are involved

For early phase, exploratory or psychosocial, behavioral intervention and observational studies the potential "adverse events" or risks are fundamentally different from risks in medical intervention trials, and may be difficult to anticipate and quantify. As Czaja et al. have highlighted, it can be challenging to apply typical DSMB definitions of adverse events in psychosocial, behavioral and exploratory studies. In some cases there are "contextual factors" that are relevant and not easily identified or considered within the framework of traditional DSMBs (4). Such challenges may also be present for observational genomic studies, particularly with the ongoing debate and emerging obligations to return individual research results and incidental findings (30–32). The EMC model provides an approach for monitoring study-related risks when assessment independent of the research team is desired, particularly in the setting of vulnerable populations and/or when risks that are non-traditional to the medical field (i.e., social, emotional or cultural) are possible. Given the inherent vulnerability of minors, an EMC can provide an excellent model for pediatric and family studies in which investigators seek to incorporate additional protection for vulnerable study participants. Even in studies in which a research team may have the sufficient expertise and experience to monitor research related risks, independent review may be desired by local IRBs or other regulatory bodies (i.e. funding agencies) and provide valuable feedback to investigators. As suggested by Czaja et al, while a formal DSMB may not be needed, some additional oversight may be desired for some studies based on their "risk profile,", such as investigations in dementia patients where higher risks may be inherently assumed (4).

Recommendation 2: Construct EMC membership based on the study design, setting and population

Obtaining relevant expertise on independent oversight boards is important to ensure appropriate review and interpretation of study-related risks (4, 10). For each study, we selected 5 member boards in the event that voting was needed, with appropriate multidisciplinary expertise in disciplines relevant to the study goals. Adolescent research should include at least one member with expertise in adolescent health or development and some studies may benefit from including members from the lay public to represent the perspectives of study participants. Multicenter studies should consider regional representation, particularly if cultural norms or regulatory requirements might differ. Depending on oversight needs and the goals of the EMC, membership could be smaller or larger to achieve the expertise necessary to support the specific study design and EMC goals. Investigators may also want to consider the racial and/or ethnic background of their study population in determining EMC composition, particularly where evidence suggests differences in risks and outcomes across certain racial and/or ethnic populations, or where potential differences in psychosocial vulnerabilities may exist.

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Recommendation 3: Define the goals of the EMC at study onset and tailor to the study population and design

Establishing the goals of the EMC at the onset of the study is important, as they can inform protocols and procedures for monitoring participant safety and provide a solid framework for evaluating study-related risks. We also found it important to maintain flexibility when establishing goals in order to individualize them for particular study designs (which differed between the qualitative SOFT I and quantitative SOFT II and LEGACY Girls studies). Consistent with Czaja et al., we recommend that the methods and procedures for monitoring risks should be tailored to the study (4) and adapted as needed to achieve the goals of the EMC (4).

Recommendation 4: Define adverse events

A key goal of independent oversight committees in clinical trials is monitoring and analyzing adverse events (6, 8, 33). Such systematic tracking and reporting of adverse events in psychosocial, behavioral intervention and observational studies is a more recent phenomenon, with guidelines being less clearly defined and a greater challenge to apply, as they were traditionally developed for biomedical research (3, 4). Consequently, the EMCs for our studies also considered the potential risks, both study-related and incidental to data collection, and provided feedback on the monitoring plans, their conduct and outcomes. Thus, we propose that an EMC can be instrumental to enhancing human subject protection for studies in which risks are non-traditional or unanticipated. As highlighted by others (3, 4, 10), we recommended that definitions of “adverse events” and approaches to monitoring are tailored to the patient population and study design.

Recommendation 5: Define protocols for data reporting and interim assessment

While the specific process of establishing DSMBs for evaluating clinical trial quality and progress may not be relevant to many psychosocial, behavioral intervention and observational studies, an assessment of the risks and benefits to study participants is nonetheless important and should be conducted at regular intervals. This is consistent with recommendations from Czaja et al, who similarly note that procedures for interim data analysis should be clearly outlined (4). Similar to a DSMB, the EMC in the SOFT I, SOFT II and the LEGACY Girls Study each provided interim assessments (once or twice annually) of the risks and benefits of the studies. As described above, the EMC reviewed monitoring procedures, events and outcomes throughout all three studies, although procedures and intervals varied based on study design and activities. Thus, we recommend that protocols for monitoring study risks and defining adverse events be tailored to study design and procedures.

Recommendation 6: Consider an EMC for multi-center studies

The NIH has deemed the function of a DSMB as particularly important in multi-center studies, as investigator responsibilities and obligations are to the local IRB only. Additionally, there can be variability in IRB assessments, recommendations and approaches to oversight across institutions (4, 8, 10, 34). Thus, an EMC may provide an independent comprehensive, study-wide oversight mechanism, providing local IRBs greater confidence

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in the protection of research participants, and simplifying local review and regulatory burdens. As suggested by others, monitoring across multiple sites could identify potential risks that are rare at any individual site, but collectively can be informative and their identification may enhance human subject protection (4, 10).

Conclusions

It is imperative for researchers to monitor the safety of all research participants to minimize associated risks. This is particularly relevant in studies involving children and adolescents, where the Common Rule mandates special attention to their risks and benefits (5). At this time, there remains limited guidance for when additional oversight is needed in studies which do not require a DSMB. Thus, these decisions are currently made by investigators or local IRBs based on their assessments of the risks of any particular study and their familiarity with alternative models. Ultimately, incorporating standard criteria and regulatory standards for independent oversight in psychosocial, behavioral intervention and observational studies could be very valuable for investigators and IRBs. An EMC is a model for independent oversight, which can be successfully implemented for psychosocial, behavioral intervention and observational studies, in which additional human subjects' safeguards are desired. We have demonstrated the feasibility and value of using this framework within the context of three child and adolescent health studies. This framework and the associated recommendations are intended to be broadly applicable and useful to investigators and IRBs, and could be incorporated into future regulatory standards to enhance the safety and completion of a wide range of research activities designed to improve the health of children, adolescents, and families.

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Implications and Contribution

It is imperative for researchers to monitor the safety of research participants, particularly in studies involving children and adolescents. The implementation of an Event Monitoring Committee provides a model for independent oversight in behavioral and observational studies involving children and adolescents, in which additional human subjects' safeguards are desired.

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Table 1

Characteristics of SOFT I, SOFT II and LEGACY Girls Studies

	SOFT I Study	SOFT II Study	LEGACY Girls Study
Study aims	To explore differences in knowledge and perceptions of breast cancer risk among girls from breast cancer families and families without breast cancer	To investigate how psychosocial adjustment and health and risk behaviors differ among girls from breast cancer families and families without breast cancer	To study epidemiologic and epigenetic pathways of childhood and adolescent exposures in relation to pubertal development, age at menarche, breast tissue characteristics, selected biomarkers, genomic DNA methylation, and the psychosocial impact of increased breast cancer susceptibility
Participants	Girls ages 11–19* years from breast cancer families and families without breast cancer Mothers (short survey)	Girls ages 11–19 years from breast cancer families and families without breast cancer Mothers (parallel survey)	Girls ages 6–13 years from breast cancer families and families without breast cancer Mothers (parallel survey)
Enrollment	N= 54 (single site) August 2009–November 2010*	N=213 (two sites) November 2010 –present**	N=1040 (five sites) October 2011– June 2013***
Study procedures	Single, semi-structured telephone interview	Quantitative surveys (baseline and 1 follow-up)	Biospecimen collection, anthropometric measures and quantitative surveys (baseline and follow-up every 6 months)
Survey Content	Knowledge and perceptions of breast cancer risk	Knowledge and perceptions of breast cancer risk Health and risk behaviors Psychosocial adjustment (reported by mother and daughter)	Knowledge and perceptions of breast cancer risk Health and risk behaviors Psychosocial adjustment (reported by mother for their daughters ages 6–13 years) and self-reported by girls ages 10–13 years) Growth and development Early life environment

* study began with girls ages 14–19 years and later was extended to younger girls ages 11–13 years

** recruitment ongoing

*** longitudinal follow-up ongoing

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Table 2

Recommendations for Implementation of an EMC

1. Consider the value of an EMC in psychosocial, behavioral interventional and observational studies when there is potential for psychosocial risks or vulnerable populations are involved
2. Construct EMC membership based on the study design, setting and population
3. Define the goals of the EMC at study onset and tailor to the study population and design
4. Define adverse events
5. Define protocols for event reporting and interim assessment
6. Consider an EMC for psychosocial-behavioral and observational multi-center studies