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Ethical approval for multicenter cohort studies on drug exposure during pregnancy: A survey among members of the European Network of Teratology Information Services (ENTIS)

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ABSTRACT

The European Network of Teratology Information Services (ENTIS) is in a privileged position to perform independent post-marketing surveillance of drugs in pregnancy. The aim of this survey was to describe the legal requirements and procedures involved in obtaining ethical approval for collaborative cohort studies. We sent a survey questionnaire to all 28 Teratology Information Services (TIS), of which 25 (89%) in 18 countries completed our questionnaire. For 15 TIS, specific research ethical approval was mandatory. The review process was estimated to last from 2 up to 16 weeks. Procedures for patients' information and consent were oral (12), written (5) or both (3). Five TIS had no requirement to inform patients and seek consent. Since data on drug exposure during pregnancy are scarce, ENTIS research efforts should be further encouraged, and procedures optimized so that legitimate ethical and legal requirements do not translate into deterrent administrative constraints and costs.

1. Introduction

The European Network of Teratology Information Services (ENTIS) is a non-profit organization founded in 1990 with the aim of coordinating Teratology Information Service (TIS) activities. ENTIS missions and goals focus on prevention, education, research, and collaboration (see www.entis-org.eu). TIS are dedicated to providing evidence-based information to patients and their caregivers regarding the safety and risks of medications and other exposures during pregnancy and breastfeeding. Furthermore, TIS staff collects patient data both during initial contact and after a follow-up period covering pregnancy outcome. Using these data from individual TIS databases, ENTIS has been successful in performing collaborative research leading to a significant number of scientific contributions regarding a variety of drugs during pregnancy [1–19]. This research activity is an important mainstay for one of the primary ENTIS goals, which is "to contribute to the primary prevention of birth defects and developmental disorders". The Organization of Teratology Information Specialists (OTIS), a similar collaborative effort of TIS in North America, is also regularly performing cohort studies on risks associated with drugs during pregnancy and lactation, and common research efforts have been accomplished in the past and are planned in the future [20,21].A variety of methodological approaches is used to assess the relation between drug exposure and fetal outcome including case reports, case-control studies, cohort studies, computerized database surveys, and analysis of pregnancy registries. Case reports are important for obtaining signals of potential drug-induced developmental toxicity for a specific drug, however with a non-negligible risk of causing false alarms [22]. Epidemiological studies are typically designed to determine whether mothers of children with a specific malformation received a given drug more often than mothers of children without the malformation (case–control studies) or whether mothers who received a specific drug during pregnancy are more likely to have malformed children than mothers who did not (cohort studies) [23]. Case-control studies are especially useful for evaluating rare outcomes but generally rely on maternal recall for exposure information, which may differ between cases and controls [22]. Cohort studies are commonly used for analyzing TIS data and even though their sample size is frequently limited,

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they have definite methodological strengths including: prospective data ascertainment, collection of precise information on exposures in terms of timing and dosage, geographical representativeness, and collection of a broad range and depth of information regarding outcome [24]. The possibility of selecting appropriate comparison groups (disease matched, unexposed pregnancies) is important. Multicenter ENTIS studies can provide comparison groups, which have been accessed in the same way as the exposed. Analysis of computerized databases, which have the advantage of accessibility to large numbers of exposed pregnancies and outcomes, often raise concerns regarding misclassification and uncertainties surrounding actual exposure and timing [22]. Pregnancy registries typically involve prospective data collection and, depending on the frequency of exposure, can accrue relatively large numbers of subjects. However, registries are sometimes limited by the absence of important information, such as the timing and dose of the exposure drug [22].

Setting up multicenter cohort study protocols like those supported by ENTIS raises specific challenges regarding regulatory approval, since the legal framework varies greatly between countries and institutions. Moreover, changes in regulatory requirements tend to increase in frequency over time. For instance, we experienced a significant delay in the publication of a collaborative ENTIS study on pregnancy outcome following maternal exposure to pregabalin [3]. This was the consequence of procedural difficulties in obtaining ethics board approval of one participating institution. Knowledge about procedures involved in obtaining ethical approval, patient consent and other legal requirements is necessary when undertaking multicenter cohort studies in order to adequately plan study timelines, submission processes and facilitate timely publication. The aim of our work was to provide an overview of requirements for ethical and competent approval for multicenter observational cohort studies among ENTIS members.

2. Material and methods

We performed a survey among all ENTIS members in February 2016. A draft of the questionnaire was elaborated and validated by the coauthors. The final version of the questionnaire was then sent by e-mail to all centers. Reminders were mailed to centers who did not respond initially.

The survey consisted of 31 specific questions with room for free text comments at the end of the questionnaire. The main issues addressed in the survey were:

- General information about the TIS
- Research ethics committee approval: legal requirements, procedures (type of ethics committee, details and duration of administrative procedures, impact on the participation in collaborative studies)
- Other required approvals (institutional review board, director of institution, study registry, database registry)
- Modalities of patient information and consent
- Data protection aspects

Survey data were analyzed using standard descriptive statistics in Microsoft Excel (2015).

3. Results

3.1. Participating centers

Of the 28 TIS, 25 (89%) completed the questionnaire. Fig. 1 shows the world map of full ENTIS members. Details of the participating TIS are listed in Table 1. Responding TIS were located in 18 countries. Among these TIS, 18 were affiliated with a hospital, 14 with a university, 3 with a private organization, and 4 with a governmental or public institution. Twelve had multiple affiliations, with a majority of double affiliations to a university and a hospital. Twenty-one TIS declared operating their own website. Across all countries covered by ENTIS, the total annual birth rate was about 1'143'000 in 2014 [25]. During the same year, TIS provided 140'363 counsels altogether (median per center 2548, range 88–25961). All but one TIS (24) responded that they collected follow-up data with their calls, accounting for 12'318 follow-ups in 2014 (median 225, range 0–4100). Pregnancy and breastfeeding counsels represented a median of 83% (range 30–100%) and 17% (range 0–40%) of inquiries, respectively. All but one TIS (24) accepted calls from healthcare professionals, 1 only from the public, and 18 from both. The majority of counsels were provided by telephone (median 77%, range 0–100%). Ten TIS also used written documents (letter/fax/report) and 13 used e-mail or other electronic messaging for their counseling. Thirteen TIS reported counseling patients during outpatient visits. Only 6 TIS reported sending cases to the national pharmacovigilance system.

Twenty-two TIS declared having contributed patient data for research purposes during the last 5 years (median 6 research projects, range 0–34) including cohort studies, case reports, case series, and multicenter studies. A total of 15 collaborative ENTIS cohort studies have been published between 2007 and 2017 including data from 14'727 pregnancies altogether (Table 2) [1–15].

3.2. Research ethics committee approval

In 15 TIS, some kind of research ethical approval was mandatory for participation in cohort studies, whereas no specific ethics review was necessary in the remaining 10 TIS (Table 3). Two TIS declared optionally submitting protocols to the ethics committee in charge. The responsible ethics committees were only local (13), only national (2) or both (2) and applied full committee (12) and fast track (4) procedures (1 unknown). The documents required by ethics committees varied greatly between TIS: standard application form (15), study protocol (16), patient/healthcare professional information material (11), patient consent form (10), and researchers' curriculum vitae (6). For one TIS this information was not available. The median estimated time to prepare the documents for the approval of a collaborative ENTIS study protocol was 6 h (range 3–72 h). In 10 TIS, the review process by the ethics committees was estimated to last up to 4 weeks. The shortest estimated period was 2 weeks and the longest 16 weeks. Thirteen TIS declared that no costs were incurred for evaluation by ethics committee. For the other TIS, fees varied between the equivalent of 200 and 1000 €. Ten TIS are requested by the research ethics committee to report back after the end of a study. The time, effort and skills usually required for applications to research ethics committee represented no problem for 4 TIS, a small problem for 8 TIS, and a problem large enough to limit participation in collaborative studies for 2 TIS.

3.3. Other approvals

Eleven TIS declared that they had to submit prospective observational study protocols to other bodies including: institutional review boards (3), directors of institution (5), study registries (3), a database registry (1), drug regulation authority (1), chief scientist office (1), and other database (1).

3.4. Patient information and consent

Procedures used to inform patients on the possibility of inclusion of case observations into prospective studies included: oral communication (12), written communication (5) or both (3). Five TIS had no requirement to inform patients and seek consent.

3.5. Data protection

Twenty TIS needed to fulfill special requirements for data collection and storage aiming at data protection. The following types of databases