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The French prospective multi-site registry on sudden unexpected infant death (OMIN): rationale and study protocol

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TITLE

The French prospective multi-site registry on sudden unexpected infant death (OMIN): rationale and study protocol

AUTHORS

Karine Levieux [1-2], Hugues Patural [3], Inge Harrewijn [4], Elisabeth Briand Huchet [5], Sophie de Visme [2], Géraldine Gallot [6], Martin Chalumeau [7,8], Christèle Gras Le Guen [1-2-7], Matthieu Hanf [2-9,] on behalf of the OMIN study group [10]

AFFILIATIONS

1 Pediatric emergency Care Unit Nantes University Hospital, Nantes, France

2 CIC1413, Nantes University Hospital, Nantes, France

3 Pediatric Intensive Care Unit Saint-Étienne University Hospital, Saint Etienne, France

4 Pediatric Intensive Care Unit Montpellier University Hospital, Montpellier, France

5 Pediatric Intensive Care Unit, Antoine Béclère University Hospital, AP-HP, Clamart, France

6 Biological Resource Center (BRC), Nantes, F-44093 Nantes University Hospital, Nantes, France

7 INSERM, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), Paris Descartes University, Paris, France.

8 Department of General Pediatrics and Pediatric Infectious Diseases, Necker-Enfants Malades Hospital, Assistance Publique-Hôpitaux de Paris, Paris Descartes University, Paris, France.

9 Inserm UMR 1181 B2PHI, Versailles Saint Quentin University, institut Pasteur, Villejuif, France

10 OMIN study group : Patricia Garcia-Meric, Laurence Fayol, Loic De Pontual, Aurélien Galerne, Anne-Marie Teychene-Coutet, Jean-Claude Netter, Gaël Sibille, Fakhreddine Maiz, Mariana Englender, Alain De Broca, Petronela Rachieru-Sourisseau, Christine Guillermet, Julia Pauls-Barsanti, Christiane Le-Bot, Anne-Sophie Trentesau, Djamel Sebbouh, Stéphanie Perez-Martin, Muriel Maegd, Anne-Pascale Michard-Lenoir, Abdelilah Tahir, Béatrice Kugener, Blandine Muanza, Odile Pidoux, Anne Borsa Dorion, Mickael Afanetti, Barbara Tisseron, Anne Rancurel, Lolita Leguay, Caroline Robin, Marie Lebeau, Béatrice Digeon,

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Bénédicte Vrignaud, Céline Farges, François Lecruit, Michel Dagorne, Jean-Luc Alessandri, Sylvain Samperi, Laurent Balu, Olivier Mory, Audrey Breining, Gilles Duthoit, Elisabeth Daussac, Yasmine Plee, Alain Chantepie, Myriam Bouillo

CORRESPONDING AUTHOR

Karine Levieux, Nantes University Hospital, Pediatric Emergency Care Unit, 9 Quai Moncousu, 44093 Nantes CEDEX 1, FRANCE; E-mail address: karine.levieux@chu-nantes.fr; Telephone number: +33 (0)240087937

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ABSTRACT

Introduction

Even after "back-to-sleep" campaigns, sudden unexpected infant death (SUID) continues to be the leading cause of death for infants 1 month to 1-year-old in developed countries, with devastating social, psychological and legal implications for families. To sustainably tackle this problem and decrease the number of sudden infant deaths, a French SUID registry was initiated in 2016 to 1) inform prevention with standardized data, 2) understand the mechanisms leading to sudden infant death and the contribution of the already known or newly suggested risk factors, and 3) gather a multidisciplinary group of experts to coordinate and develop innovative and urgent research in the SUID area.

Methods and analysis

This observational multi-site prospective observatory includes all cases of sudden unexplained deaths in children younger than 2 years occurring in the French territory covered by the 34 participating French referral centers. From these cases, various data concerning socio-demographic conditions, death scene, personal and family medical history, parental behaviors, sleep environment, clinical examinations, biological and imagery investigations, and autopsy are systematically collected. These data will be complemented as of 2018 with a biobank of diverse biological samples (blood, hair, urine, feces and cerebrospinal fluid), with other administrative health-related data (health claim reimbursements and hospital admissions) and socio-environmental data. Insights from exploratory descriptive statistics and thematic analysis will be combined for the design of targeted strategies to effectively reduce preventable infant deaths.

Ethics and dissemination

The Observatoire National des Morts Inattendues du Nourrisson (OMIN) registry was approved in 2015 by the French Data Protection Authority in clinical research (CNIL: no.

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915273) and by an independent ethics committee (GNEDS: no. 2015-01-27). Results will be discussed with associations of families affected by SUID, caregivers, funders of the registry, medical societies and researchers and will be submitted to international peer-reviewed journals and presented at international conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- The French SUID registry is the first research program combining French SUID referral centers and a multidisciplinary group of experts.
- The French SUID registry innovative design combines prospective data concerning sociodemographic conditions, death scene, medical history, parental behaviors, sleep environment, clinical examinations and autopsy findings along with biological samples and other administrative health-related data to yield a detailed description of SUID cases.
- As far as possible, the French SUID registry is using standardized data to facilitate future collaborations with other countries to share best practice, monitor progress, and achieve statistical power for future investigations.
- The results will help in the design of targeted strategies to effectively reduce preventable infant deaths.
- The potential limitations of the French SUID registry are ascertaining the exhaustive inclusion of all SUID cases occurring in France as well as the lack of a concomitant control population.

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INTRODUCTION

Sudden unexpected infant death (SUID), a devastating event for families, is defined as death in an infant less than 1 year old that occurs suddenly and unexpectedly and whose cause is not immediately obvious before investigation [1]. After case investigation, including a scene investigation, a review of clinical history, and an autopsy, SUID can be attributed to various causes. Death is classified as a sudden infant death syndrome (SIDS) when the thorough postmortem examination fails to identify its cause [2].

Much research has been conducted to identify and control risk factors leading SUID to be conceptualized as a multifactorial disorder with multiple mechanisms causing or predisposing its occurrence. A "triple-risk" hypothesis (child vulnerability, critical period in development, and exogenous stress factors) has been proposed [3]. Subsequent to the discovery of the prone sleep position as a major risk factor, “back-to-sleep” prevention campaigns were conducted in the early 1990s and led to a huge decrease in SUID incidence in many countries. However, in the post “back-to-sleep” era, SUID continues to be the first cause of death for infants 1 month to 1 year old in developed countries, and strategic actions are still needed to sustainably tackle this devastating event [4].

An international consensus, The Global Action and Prioritization of Sudden Infant Death (GAPS) Project, has recently provided the international SUID research community with a list of shared research priorities to more effectively work toward explaining and reducing the number of sudden infant deaths [5]. Three main themes emerged: 1) a better understanding of mechanisms underlying SUID, 2) ensuring best practices in data collection, management and sharing, and 3) a better understanding of target populations and more effective communication of known risk factors. To meet these challenges, the creation of innovative national SUID registries systematically collecting standardized data for every SUID case along with biological samples seems an essential prerequisite.

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Accordingly, in 2015, 34 French SUID Referral Centers in collaboration with the National Association of Referral Centers for SUID (ANCReMIN) initiated a French national registry, Observatoire National des Morts Inattendues du Nourrisson (OMIN) to prospectively collect for all French SUID cases a large variety of socio-environmental, behavioral, clinical, radiological and autopsy data simultaneously with biological samples as well as other health-related administrative data (health claim reimbursements and hospital admissions) concerning children less than 2 years old and their mothers. The global objective of this registry is to sustainably decrease the number of sudden infant deaths by 1) informing prevention with standardized data; 2) understanding the mechanisms leading to sudden infant death, including the contribution of the already known or newly suggested risk factors; and 3) gathering a multidisciplinary group of experts to coordinate and develop research in the SUID area. This report aims to describe the methodology used to establish and manage this registry.

DESIGN

Study design and population

The French SUID registry is an observational prospective registry that over at least a 10-year period, aims to include all SUID cases occurring in the French metropolitan territory plus two overseas islands: La Martinique (Caribbean Sea) and La Réunion (Indian Ocean) (Figure 1). Thirty-four French SUID referral centers are participating in this registry.

Because in France, a SUID case is legally defined as the sudden unexpected death of a child less than 2 years old [6], all children younger than 2 years dying in the context of SUID are eligible for the registry. Once both parents are informed that participating is voluntary and anonymous, data for all children for whom parents give informed written consent are included.

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Data collection

The OMIN is based on a continuous and prospective record of pre-specified and standardized information concerning the examinations that should be performed with a SUID case as recommended by the French national health authority [6]. The data collection depends on the SUID case trajectory after death as well as the willingness of parents to participate. Data are gathered from two different sources: 1) the mobile intensive care unit (MICU) initially in charge of the SUID case on the death scene, and 2) the SUID referral center performing the postmortem exploration to identify the cause of death (Figure 2). Additionally, other health-related and socio-environmental data will be secondary linked as of 2018 to the case in the OMIN database. To ensure that all SUID cases are recorded in the registry, data from the MICU concerning dead children transported directly to the mortuary and not under the control of a referral center are also collected. In case of forensic investigations (not performed by the referral centers) requested by the Court of Justice, only the MICU data are available. Data collected during the forensic investigation are recorded a second time when the legal procedures are finalized. A minimal set of anonymous data (age at death and gender) are also gathered when at least one of the parents refuses to participate in the registry.

Data from MICU and SUID referral centers

Data collected by MICU and SUID referral centers are related to the social and demographic status of children and their parents, personal and family medical history, antenatal and current parental behaviors, child feeding, death scene, usual and death sleep environment, nature and results of clinical examinations at the death scene and the referral center, nature and results of additional clinical examinations performed in the referral center, and classification of SUID cases by the medical team based on a national classification and that from Fleming et al.[7] (Table 1).

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Biological sample collection

The collection of biological samples is essential for the SUID research community to better examine the intrinsic mechanisms leading to death and how they interact with environmental risk factors (priority 1 of the GAPS Project), identify biomarkers to help pathologists determine the cause of death (priority 5 of the GAPS Project), and understand the role of genetic factors in SUID risk (priority 6 of the GAPS Project). Accordingly, blood, hair, urine, feces and cerebrospinal fluid (CSF) samples will be collected as of 2018 from all included SUID cases during the post-mortem examination performed at the SUID referral center. These biological samples will be stored in a network of 28 participating Biological Resource Centers. For blood, a dried blood spot as well as 20 aliquots of blood (2 ml) will be stored for each child: 8 total blood aliquots (EDTA), 4 plasma aliquots (EDTA), 4 buffy-coat aliquots (EDTA), and 4 serum aliquots (Dry SST). Five aliquots for urine, 1 for CSF and 3 for feces will be kept. A lock of hair and 2 feces bottlebrushes will be additionally stored. Standardized procedures for biological sample collection will be used, including standardized blood sampling, transport from each site to the central laboratory (< 24 h), aliquoting in cryotubes, and storage temperature (ambient temperature, -80°C or -196°C depending on the nature of the biological sample). For timely follow-up of collected biological samples as well as their availability, a central database will be created.

Linkage with secondary sources of data

The completion of a death certificate by a physician is compulsory in France on the occurrence of death. Data from this certificate are gathered by the French registry of death causes (CépiDc) for the whole French population, by gender, age, country of birth and underlying cause of death coded according to the International Classification of Diseases, 10th

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Revision (ICD-10). Legal authorization was obtained from CépiDc to gather information concerning all deaths in children less than 2 years old for calculating the exhaustiveness of inclusions in the French SUID registry.

Similarly, health related information concerning infants and their mothers will be gathered as of 2018 in the French SUID registry from the French national health insurance information system (Système national d'information inter-régimes de l'Assurance maladie, SNIIR-AM) and the French hospital discharge database (Programme de Médicalisation des Systèmes d'Information, PMSI). SNIIR-AM covers the entire French population (65.3 million inhabitants) and contains exhaustive data on all reimbursements for health-related expenditures [8,9] including medicinal products such as drugs and outpatient medical and nursing care prescribed or performed by healthcare professionals. PMSI provides detailed medical information on all admissions to French public and private hospitals, including dates of hospital admission and hospital discharge, discharge diagnosis ICD-10 codes, and medical procedures during the hospital stay. Data in PMSI and SNIIR-AM were recently made publically available for epidemiological pharmacological and epidemiological studies [10,11].

To allow for case–control studies to identify risk factors for SUID, data access will be requested in a near future from the Étude longitudinale française depuis l'enfance (ELFE) cohort to use included participants as a control group. ELFE was initiated in 2011 and is a nationally representative cohort of 20,000 children followed from birth to adulthood by use of a multidisciplinary approach to thoroughly characterize the relation between environmental exposures and the socioeconomic context on health and behaviors [12].

Population data needed to calculate incidence rates as well as socio-environmental information concerning the place of residence/death will also be gathered from the French National Institute of Statistics and Economic Studies [13].

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DATA MANAGEMENT AND DATA ANALYSIS

This multicenter registry relies on a Web-based system with data being entered into a central database. The system provides security with protected access and complies with French safety policy [14]. Data entry and validation is performed as a continuous process. For each SUID case, data extracted from MICU and SUID referral center records (approximatively 300 variables) are entered directly online by the medical team in charge of the case. A national project manager continuously controls data completeness and validity and notifies the local medical team in case of discrepancies or incomplete data. Routine permanent quality controls, based on regular on-site inspections, are planned, including training of personnel, compliance with study procedures as well as control of data completeness and validity. Automatic data quality controls are performed periodically to control for missing data and value ranges. Once data from the CépiDc will be available, recorded data will be compared with those from death certificates to estimate the exhaustiveness of the inclusions in the database. Finally, linkages with previously described secondary data sources will be planned once a year.

In this registry, the number of SUID cases occurring in the French territory per year will determine the recruitment size. On the basis of the referral centers' experience as well as the last national estimation performed in 2014 by the French registry of death causes [15], we expect to recruit at least 300 SUID cases each year. A final sample size of about 3000 cases is thus expected for a study period of 10 years.

Confidence intervals, means, standard deviations and frequency distributions will be calculated for all measures. Available data for cases with parental refusals and without a SUID referral center in charge will be compared with cases with a SUID referral center in charge. Survival analyses will be used to analyze time-to-event data such as death to identify factors associated with early or late SUID. Multivariable binomial regressions will be used to compare subgroups of SUID children or control children. Multilevel multivariate statistical

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modeling will also be used to simultaneously study individual and higher-level predictors of outcomes (such as place of residence characteristics). Because the hypothesis that missing values are missing at random is plausible for only children with a SUID referral center in charge, multiple imputation will be used to avoid bias due to missing data for these children. To counteract the potential problem of multiple comparisons, adjustment for statistical significance will be performed when needed. Depending on data and the statistical power available, various other statistical models will also be implemented.

ETHICS AND DISSIMINATION

The registry was registered by the French data protection authority in clinical research (Commission Nationale de l'Informatique et des Libertés, CNIL; no. 915273) and approved by an ethics committee (Groupe Nantais d'Ethique dans le Domaine de la Santé, no. 2015-01-27). This project is based on a network that includes the French non-governmental national association of referral centers for SUID (Association Nationale des Centres Référents de la Mort Inattendue du Nourrisson, ANCReMIN), 34 governmental French medical referral centers in charge of the dead children and their families, Nantes University Hospital, the Nantes clinical investigation center (CIC 1413) and the Sorbonne Paris Cité center of research in epidemiology and statistics (UMR-1153). All these partners are represented in a steering committee responsible for the organization of the registry. A coordination unit is in charge to effectively manage the registry and to implement recommendations from the steering committee. Similarly, a scientific committee was created. This committee is responsible for validating all scientific projects from the registry. Data are available for analysis after validation by the scientific committee according to a validated chart of data access. Interested researchers have to comply with the French legislation (i.e., apply for authorization from the CNIL for treatment of personal health data). Research projects have also to be approved by an

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independent ethics committee. Scientific use of health insurance claims data requires individual accreditation from the data owner, the French national health insurance.

Results will be discussed with associations of families affected by SUID, caregivers, funders of the registry, medical societies and researchers and will be submitted to international peer-reviewed journals and presented at international conferences.

DISCUSSION

The systematic collection of a large variety of socio-environmental, behavioral, clinical, imaging and autopsy data simultaneously with biological samples and administrative data concerning both the children and their mothers appeared critical to study or sustainably prevent SUID deaths in the post "back-to-sleep" era. To our knowledge, this is the first prospective registry specifically designed to respond to this issue even if large population-based registries with less variety of collected data already exist in other countries [16,17]. Because collaboration with such countries is imperative to share best practices, monitor progress, and achieve statistical power for future investigations [5], the OMIN involves as far as possible standardized data to facilitate international collaborations such as meta-analyses or original or replication studies.

To be fully operational and to respond to its objectives, the registry will have to manage several challenges. The first will be to recruit a control population simultaneously with SUID cases for risk-factor studies. Indeed, although the already existing ELFE cohort is a potential way to recruit control children, several exposures are lacking in this cohort and the risk of biased selections may not be ascertained from this data source. The second challenge is to ensure the exhaustiveness of including all SUID cases occurring in the French territory. Two French referral centers currently do not participate in the OMIN. Also, preliminary tests seem to indicate a possible under-inclusion in several participating centers. Data from the

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French registry of death causes, when available, will help better quantify the magnitude of this potential bias and implement corrective measures. The third challenge will be to sustainably maintain both the mobilization of all medical and health actors and caregivers as well as public and private funding, which are essential elements for the success of this project.

In the short-term, this registry has the potential to provide an effective response to the SUID major public health issue by identifying underlying mechanisms that can be prevented and by sharing high-quality data to inform best practices and the accurate classification of SUID deaths. At the same time, such results will help in mobilizing program planners and policy makers and in designing targeted strategies to effectively reduce preventable infant deaths.

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AUTHORS' CONTRIBUTIONS

Dr Karine Levieux conceptualized and designed the study and wrote the initial draft of this article.

Matthieu Hanf conceptualized and designed the study and wrote the initial draft of this article with Dr K. Levieux.

Pr Hugues Patural, Dr Elisabeth Briand Huchet, Dr Inge Harrewijn, Sophie de Visme, Dr Géraldine Gallot, Pr Martin Chalumeau, Pr Christèle Gras-Le Guen and the OMIN study group helped in the conceptualization and design of the study and critically reviewed this article.

Pr Christèle Gras-Le Guen is the guarantor of this article.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTEREST

All authors have no conflicts of interest to disclose.

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Figure 1: Localization of the 34 referral centers participating in the French SUID registry

Figure 2: Sudden unexpected infant death management in France and data collection in the French SUID registry

MICU: mobile intensive care unit; ELFE, Étude longitudinale française depuis l'enfance

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Table 1: Data collected in the French SUID registry

Collected data	Data sources			
	MICU	Referral center	Forensic institute	Others
Social and demographic conditions				
Date and place of birth (child)	X	X		
Gender (child)	X			
Nationality (child and parents)		X		
Ethnicity (child and parents)		X		
Age (child and parents)		X		
Educational level (parents)		X		
Employment status (parents)		X		
Marital status (parents)		X		
Socioeconomic level (parents)		X		
Household composition		X		
Type of social security benefits (parents)		X		
Residency address	X			
Personal and family medical history				
Multiple birth		X		
Gestational age		X		
Birth weight		X		
Small for gestational age		X		
APGAR score at 10 min		X		
Other personal significant events during the perinatal period and early infancy		X		
History of SUID and other sudden deaths in the family		X		
Consanguinity between parents		X		
Vaccination history		X		
Significant medical events in the 72h preceding the death		X		
Significant medications in the 72h preceding the death		X		
Antenatal and current parental behaviors				
Smoking		X		
Alcohol consumption		X		
Other drug consumption		X		
Infant feeding				
Breastfeeding		X		
Last meal before death	X			
Death scene				
Date and time of death	X			
Place of death (address)	X			
Time of last contact	X			
Time of discovery	X			
Arrival time of MICU	X			
Usual and death sleep environment				
Sleep place	X			
Type of surface	X			
Sleep position last placed/found	X			
Head position	X			
Presence and type of objects on the sleep surface	X			

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Collected data	Data sources			
	MICU	Referral center	Forensic institute	Others
Thumb and pacifier use	X			
Room heat	X			
Infant dressing	X			
Room sharing	X			
Nature and results of clinical examinations				
Skin appearance	X	X	X	
Body temperature	X	X	X	
Weight	X	X	X	
Length	X	X	X	
Resuscitation maneuvers	X	X		
Signs of autonomic dysfunction	X	X	X	
Blood chemistry		X	X	
Hematology tests		X	X	
Lumbar puncture		X	X	
Microbiology		X	X	
Eye fundi		X	X	
Imagery investigations (CT scan, MRI)		X	X	
Autopsy		X	X	
Classification of SUID cases by the medical team (Fleming)		X		
Biological samples				
Blood, hair, urine, feces, and cerebrospinal fluid		X		
Other data				
History of health claim reimbursements (child and mother)				X
History of hospital admissions (child and mother)				X
Death certificate information				X
Geocoding of the residency/death address				X
Urbanicity of residency/death address				X
Deprivation index of residency/death address				X
Altitude of residency/death address				X

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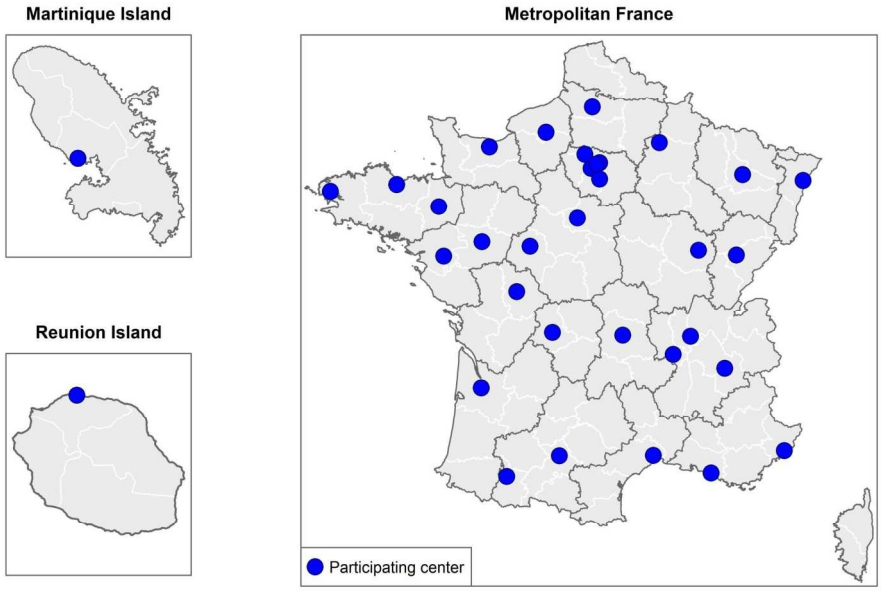

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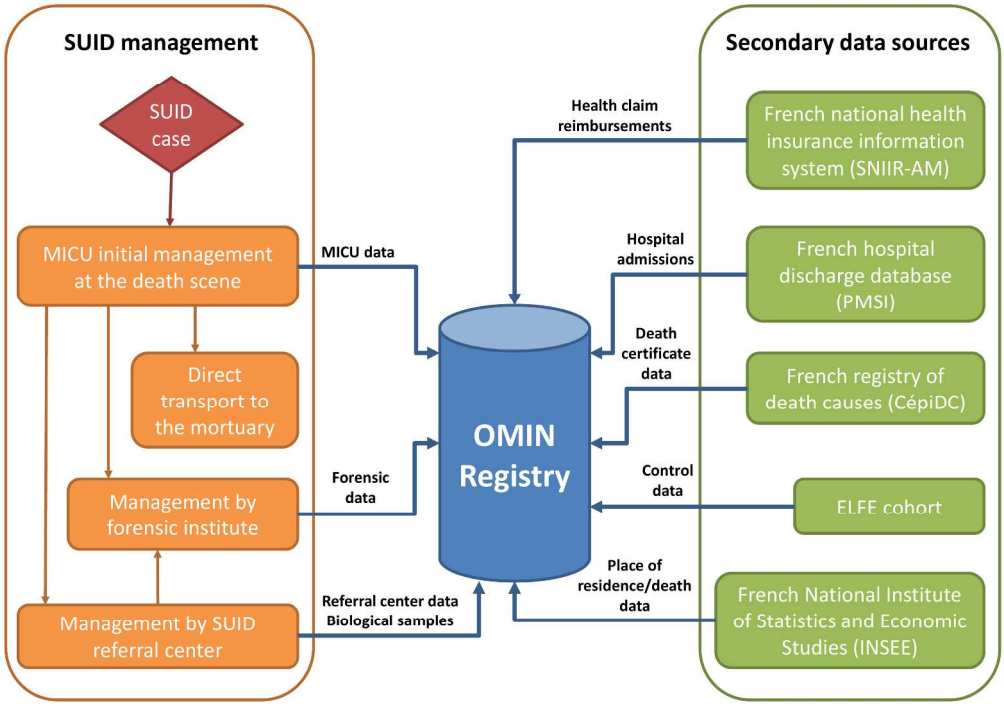

MICU: mobile intensive care unit; ELFE, Étude longitudinale française depuis l'enfance

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym : OK
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry : OK
	2b	All items from the World Health Organization Trial Registration Data Set: NA
Protocol version	3	Date and version identifier : OK
Funding	4	Sources and types of financial, material, and other support : OK
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors : OK
	5b	Name and contact information for the trial sponsor : NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities : NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) : OK
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention : OK
	6b	Explanation for choice of comparators : OK
Objectives	7	Specific objectives or hypotheses : OK
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) : OK

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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained : OK
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) : OK
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered : NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) : NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) : NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial : NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended : NA
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) : NA
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations : NA
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size : OK

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions : NA

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned : NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions : OK
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how : NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial : NA
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol : OK
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols : OK
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol : OK
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol : OK
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) : OK
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) : OK
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed : OK

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial : OK
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct : NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor : OK

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval : OK
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) : NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) : OK
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable : OK
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial : OK
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site : OK
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators : OK
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation : OK
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions : OK
	31b	Authorship eligibility guidelines and any intended use of professional writers : NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code : NA

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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates : OK
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable : OK

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Note d'information pour la participation à la recherche
« Observatoire Morts Inattendues du nourrisson et biocollection»

Titre abrégé : OMIN

Médecin Coordonnateur de l'Observatoire

Nom : LEVIEUX Karine

Service : Urgences pédiatriques

Adresse : Hôpital Mère Enfant 9 Quai Moncousu 44093 Nantes Cedex

Téléphone : 02 40 08 38 06

Courriel : karine.levieux@chu-nantes.fr

Responsable de la recherche

Nom : CHU de Nantes

Adresse : 5, allée de l'île Gloriette, 44093 NANTES

Principaux contacts : Secrétariat Bureau recherche

Téléphone : 02 53 48 28 35 (secrétariat bureau recherche)

Ce document est remis au représentant du patient

Un exemplaire est conservé dans le dossier médical

Madame, Monsieur,

Nous savons à quel point la perte de votre enfant est douloureuse et c'est dans ce contexte difficile que nous souhaitons vous présenter notre projet.

A ce jour en France, il existe trop peu de données disponibles concernant la Mort Inattendue du Nourrisson (MIN). L'Association Nationale des Centres Référents de la Mort Inattendue du Nourrisson (ANCReMIN) a donc décidé de créer en 2014 un Observatoire national (OMIN) pour regrouper l'ensemble des familles concernées par ces décès. Cet observatoire a pour objet principal de collecter des données épidémiologiques fiables, nationales, précises et actualisées dans ce domaine. Il soutient également la réalisation de protocoles de recherches scientifiques visant à explorer les causes possibles des décès et à repérer les facteurs de risques potentiellement évitables et proposer de nouveaux messages de prévention.

Vous êtes bien entendu libre d'accepter ou de refuser de participer à l'observatoire qui vous est présenté. Si vous acceptez, vous resterez à tout moment libre de changer d'avis sans avoir à

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vous justifier. Si vous refusez de participer, les données concernant votre enfant ne seront pas utilisées pour cet observatoire et resteront strictement destinées à un usage médical.

Si vous acceptez de participer, le médecin qui a pris en charge votre enfant collectera les informations nécessaires pour l'observatoire. Ces informations seront recueillies sur la Plateforme d'Echange entre les Professionnels de Santé « PEPS », plateforme internet nationale et sécurisée.

Les données nominatives recueillies afin de permettre la saisie ultérieure des résultats d'examens et seront anonymisées dans le cadre de recherches cliniques ou épidémiologiques. Vos coordonnées (ville et code postal du lieu d'habitation) seront également colligées : seuls les professionnels de santé qui ont pris en charge votre enfant auront accès à ces informations sous la responsabilité du médecin coordonnateur de l'OMIN.

En plus des données médicales de votre enfant, certaines informations concernant vos habitudes de vie, votre niveau socio-économique, votre origine ethnique et des pathologies maternelles pourront être demandées et colligées.

En complément, et afin d'être le plus exhaustif possible, nous souhaitons aussi recueillir des informations auprès des Caisses d'Assurance Maladie concernant les traitements, les hospitalisations, les soins et les médicaments reçus par la maman pendant la grossesse et par votre enfant. Ces données pourraient par exemple nous permettre d'étudier l'impact de la prise de certains traitements médicamenteux dans la survenue des Morts Inattendues du Nourrisson. Sous réserve de votre accord, ces données pourront être transférées à l'équipe OMIN dans le plus strict respect des règles de confidentialité.

Lors de l'examen médical de votre enfant, des échantillons de produits biologiques sont également recueillis (sang, urine, cheveux, liquide céphalo-rachidien et selles). Au moment du recueil, ces échantillons sont 'anonymisés' (codés de façon à ne fournir aucune indication sur votre identité) puis conservés dans un 'centre de ressources biologiques' (ou banque de collections biologiques) en vue de réaliser des dosages. Ces échantillons pourront, par exemple, être utilisés pour mesurer la présence de polluants de l'environnement, de nutriments ou d'agents infectieux. La finalité de ces analyses est de mieux comprendre l'impact de l'exposition à certains facteurs sur la survenue du décès des enfants, dans le but d'améliorer la prévention sur les Morts Inattendues du Nourrisson.

Il faut noter que les dosages réalisés dans le cadre de l'OMIN sont effectués en complément de ceux nécessaires au bilan clinique. Ces résultats ne sont pas communiqués à l'exception de ceux qui sont informatifs pour votre propre santé ou celle de vos enfants ou futurs enfants et qui peuvent donner lieu à un diagnostic et une prise en charge médicale particulière.

Les échantillons biologiques (notamment le sang) permettent de récupérer un échantillon d'ADN (matériel génétique) qui sera conservé, également après anonymisation, en vue de réaliser ultérieurement des analyses génétiques. Ces analyses génétiques auront pour seul but de rechercher des variations spécifiques au niveau de certains gènes qui pourraient être des facteurs de prédisposition à la Mort Inattendue du Nourrisson.

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Pour ce recueil d'échantillons biologiques, un formulaire spécifique d'information et de recueil de consentement vous est présenté en parallèle du présent document. Vous êtes également libre d'accepter de participer ou non à cette biocollection comme au recueil des autres données recueillies dans le cadre de l'OMIN.

Conformément à la loi, vous disposez à tout moment, et par l'intermédiaire du médecin de votre enfant, d'un droit d'accès, d'opposition et de rectification des données enregistrées sur informatique..

Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées et d'être traitées dans le cadre de cette recherche. Vous pouvez exercer vos droits d'accès et de rectification auprès du Docteur mentionné au début de ce document quand vous le souhaitez.

Cet Observatoire a reçu une autorisation de la Commission Nationale Informatique et Libertés (CNIL).

Cet Observatoire ainsi que le présent document ont été présentés au Groupe Nantais d'éthique dans le domaine de la Santé GNEDS.

Le médecin qui vous a proposé la participation à l'OMIN et qui vous a donné oralement toutes les informations nécessaires peut répondre à toutes vos questions.

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A compléter par les titulaires de l'autorité parentale	
Je soussignée : Prénom/Nom : …… …… …… mère de l'enfant (ou représentant légal), accepte : • que mes données nominatives et celles de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** • que les données démographiques, médicales, et paramédicales de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** Date : ……./……/……. Signature :	Je soussigné : Prénom/Nom : …….. …… …… père de l'enfant (ou représentant légal), accepte : • que mes données nominatives et celles de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** • que les données démographiques, médicales, et paramédicales de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** Date : ……./……/……. Signature :
Je soussigné(e) le Docteur ou Professeur : Prénom/Nom : …… Avoir informé ce jour les parents de l'enfant (Prénom/Nom) : …… sur l'Observatoire sur la Mort Inattendue du Nourrisson, d'avoir répondu à toutes leurs questions et d'avoir recueilli leur consentement libre et éclairé. Date : ……./……/……. Signature :	

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Merci de conserver l'original du consentement signé et d'en donner une copie aux parents

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BMJ Open

The French prospective multi-site registry on sudden unexpected infant death (OMIN): rationale and study protocol

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SCHOLARONE™
Manuscripts

TITLE

The French prospective multi-site registry on sudden unexpected infant death (OMIN): rationale and study protocol

AUTHORS

Karine Levieux [1-2], Hugues Patural [3], Inge Harrewijn [4], Elisabeth Briand Huchet [5], Sophie de Visme [2], Géraldine Gallot [6], Martin Chalumeau [7,8], Christèle Gras Le Guen [1-2-7], Matthieu Hanf [2-9,] and OMIN study group [10]

AFFILIATIONS

1 Pediatric emergency Care Unit Nantes University Hospital, Nantes, France

2 CIC1413, Nantes University Hospital, Nantes, France

3 Pediatric Intensive Care Unit Saint-Étienne University Hospital, Saint Etienne, France

4 Pediatric Intensive Care Unit Montpellier University Hospital, Montpellier, France

5 Pediatric Intensive Care Unit, Antoine Béclère University Hospital, AP-HP, Clamart, France

6 Biological Resource Center (BRC), Nantes, F-44093 Nantes University Hospital, Nantes, France

7 INSERM, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), Paris Descartes University, Paris, France.

8 Department of General Pediatrics and Pediatric Infectious Diseases, Necker-Enfants Malades Hospital, Assistance Publique-Hôpitaux de Paris, Paris Descartes University, Paris, France.

9 Inserm UMR 1181 B2PHI, Versailles Saint Quentin University, institut Pasteur, Villejuif, France

10 OMIN study group : Patricia Garcia-Meric, Laurence Fayol, Loic De Pontual, Aurélien Galerne, Anne-Marie Teychene-Coutet, Jean-Claude Netter, Gaël Sibille, Fakhreddine Maiz, Mariana Englender, Alain De Broca, Petronela Rachieru-Sourisseau, Christine Guillermet, Julia Pauls-Barsanti, Christiane Le-Bot, Anne-Sophie Trentesau, Djamel Sebbouh, Stéphanie Perez-Martin, Muriel Maegd, Anne-Pascale Michard-Lenoir, Abdelilah Tahir, Béatrice Kugener, Blandine Muanza, Odile Pidoux, Anne Borsa Dorion, Mickael Afanetti, Barbara Tisseron, Anne Rancurel, Lolita Leguay, Caroline Robin, Marie Lebeau, Béatrice Digeon,

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Bénédicte Vrignaud, Céline Farges, François Lecruit, Michel Dagorne, Jean-Luc Alessandri, Sylvain Samperi, Laurent Balu, Olivier Mory, Audrey Breining, Gilles Duthoit, Elisabeth Daussac, Yasmine Plee, Alain Chantepie, Myriam Bouillo

CORRESPONDING AUTHOR

Karine Levieux, Nantes University Hospital, Pediatric Emergency Care Unit, 9 Quai Moncousu, 44093 Nantes CEDEX 1, FRANCE; E-mail address: karine.levieux@chu-nantes.fr; Telephone number: +33 (0)240087937

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ABSTRACT

Introduction

Even after "back-to-sleep" campaigns, sudden unexpected infant death (SUID) continues to be the leading cause of death for infants 1 month to 1-year-old in developed countries, with devastating social, psychological and legal implications for families. To sustainably tackle this problem and decrease the number of sudden unexpected infant deaths, a French SUID registry was initiated in 2015 to 1) inform prevention with standardized data, 2) understand the mechanisms leading to sudden unexpected infant death and the contribution of the already known or newly suggested risk factors, and 3) gather a multidisciplinary group of experts to coordinate and develop innovative and urgent research in the SUID area.

Methods and analysis

This observational multi-site prospective observatory includes all cases of sudden unexpected deaths in children younger than 2 years occurring in the French territory covered by the 34 participating French referral centers. From these cases, various data concerning socio-demographic conditions, death scene, personal and family medical history, parental behaviors, sleep environment, clinical examinations, biological and imagery investigations, and autopsy are systematically collected. These data will be complemented as of 2018 with a biobank of diverse biological samples (blood, hair, urine, feces and cerebrospinal fluid), with other administrative health-related data (health claim reimbursements and hospital admissions) and socio-environmental data. Insights from exploratory descriptive statistics and thematic analysis will be combined for the design of targeted strategies to effectively reduce preventable infant deaths.

Ethics and dissemination

The Observatoire National des Morts Inattendues du Nourrisson (OMIN) registry was approved in 2015 by the French Data Protection Authority in clinical research (CNIL: no.

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915273) and by an independent ethics committee (GNEDS: no. 2015-01-27). Results will be discussed with associations of families affected by SUID, caregivers, funders of the registry, medical societies and researchers and will be submitted to international peer-reviewed journals and presented at international conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- The French SUID registry is the first research program combining French SUID referral centers and a multidisciplinary group of experts.
- The French SUID registry innovative design combines prospective data concerning sociodemographic conditions, death scene, medical history, parental behaviors, sleep environment, clinical examinations and autopsy findings along with biological samples and other administrative health-related data to yield a detailed description of SUID cases.
- As far as possible, the French SUID registry is using standardized data to facilitate future collaborations with other countries to share best practice, monitor progress, and achieve statistical power for future investigations.
- The results will help in the design of targeted strategies to effectively reduce preventable infant deaths.
- The potential limitations of the French SUID registry are ascertaining the exhaustive inclusion of all SUID cases occurring in France as well as the lack of a concomitant control population.

WORD COUNT: 2550

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INTRODUCTION

Sudden unexpected infant death (SUID), a devastating event for families, is defined as death in an infant less than 1 year old that occurs suddenly and unexpectedly and whose cause is not immediately obvious before investigation [1]. After case investigation, including a scene investigation, a review of clinical history, and an autopsy, SUID can be attributed to various causes. Death is classified as a sudden infant death syndrome (SIDS) when the thorough postmortem examination fails to identify its cause [2].

Much research has been conducted to identify and control risk factors leading SUID to be conceptualized as a multifactorial disorder with multiple mechanisms causing or predisposing its occurrence. A "triple-risk" hypothesis (child vulnerability, critical period in development, and exogenous stress factors) has been proposed [3]. Subsequent to the discovery of the prone sleep position as a major risk factor, “back-to-sleep” prevention campaigns were conducted in the early 1990s and led to a huge decrease in SUID incidence in many countries. However, in the post “back-to-sleep” era, SUID continues to be the first cause of death for infants 1 month to 1 year old in developed countries, and strategic actions are still needed to sustainably tackle this devastating event [4].

An international consensus, The Global Action and Prioritization of Sudden Infant Death (GAPS) Project, has recently provided the international SUID research community with a list of shared research priorities to more effectively work toward explaining and reducing the number of sudden infant deaths [5]. Three main themes emerged: 1) a better understanding of mechanisms underlying SUID, 2) ensuring best practices in data collection, management and sharing, and 3) a better understanding of target populations and more effective communication of known risk factors. To meet these challenges, the creation of innovative national SUID registries systematically collecting standardized data for every SUID case along with biological samples seems an essential prerequisite [6].

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Accordingly, in 2015, 34 French SUID Referral Centers in collaboration with the National Association of Referral Centers for SUID (ANCReMIN) initiated a French national registry, Observatoire National des Morts Inattendues du Nourrisson (OMIN) to prospectively collect for all French SUID cases a large variety of socio-environmental, behavioral, clinical, radiological and autopsy data simultaneously with biological samples as well as other health-related administrative data (health claim reimbursements and hospital admissions) concerning children less than 2 years old and their mothers. The global objective of this registry is to sustainably decrease the number of sudden infant deaths by 1) informing prevention with standardized data; 2) understanding the mechanisms leading to sudden infant death, including the contribution of the already known or newly suggested risk factors; and 3) gathering a multidisciplinary group of experts to coordinate and develop research in the SUID area. This report aims to describe the methodology used to establish and manage this registry.

DESIGN

Study design and population

The French SUID registry is an observational prospective registry that over at least a 10-year period (2015-2025), aims to include all SUID cases occurring in the French metropolitan territory plus two overseas islands: La Martinique (Caribbean Sea) and La Réunion (Indian Ocean) (Figure 1). Thirty-four French SUID referral centers are participating in this registry.

Because in France, a SUID case is legally defined as the sudden unexpected death of a child less than 2 years old [7], all children younger than 2 years dying in the context of SUID are eligible for the registry. Once all the persons who have parental authority (often one or both parents) are informed that participating is voluntary, data for all children for whom all the persons who have parental authority give informed written consent are included. To ensure completeness in the registry, SUID cases for which at least one of the persons who have

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parental authority refuses to participate in the registry are recorded with a minimal set of totally anonymous data (reason for refusal, gender and age at death)

Data collection

The OMIN is based on a continuous and prospective record of pre-specified and standardized information concerning the examinations that should be performed with a SUID case as recommended by the French national health authority [7]. The data collection depends on the SUID case trajectory after death as well as the willingness of parents with parental authority to participate. Data are gathered from two different sources: 1) the mobile intensive care unit (MICU) initially in charge of the SUID case on the death scene, and 2) the SUID referral center performing the postmortem exploration to identify the cause of death (Figure 2). Additionally, other health-related and socio-environmental data will be secondary linked as of 2018 to the case in the OMIN database. To ensure that all SUID cases are recorded in the registry, data from the MICU concerning dead children transported directly to the mortuary and not under the control of a referral center are also collected. In case of forensic investigations (not performed by the referral centers) requested by the Court of Justice, only the MICU data are available. Data collected during the forensic investigation are recorded a second time when the legal procedures are finalized. A resume of the timeline and sources of data collection is presented in Figure 3.

Data from MICU and SUID referral centers

Data collected by MICU and SUID referral centers are related to the social and demographic status of children and their parents, personal and family medical history, antenatal and current parental behaviors, child feeding, death scene, usual and death sleep environment, nature and results of clinical examinations at the death scene and the referral center, nature and results of additional clinical examinations performed in the referral center, and classification of SUID

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cases by the medical team based on a national classification and that from Fleming et al.[8] (Table 1).

Biological sample collection

The collection of biological samples is essential for the SUID research community to better examine the intrinsic mechanisms leading to death and how they interact with environmental risk factors (priority 1 of the GAPS Project), identify biomarkers to help pathologists determine the cause of death (priority 5 of the GAPS Project), and understand the role of genetic factors in SUID risk (priority 6 of the GAPS Project). Accordingly, blood, hair, urine, feces and cerebrospinal fluid (CSF) samples will be collected as of 2018 from all included SUID cases during the post-mortem examination performed at the SUID referral center. These biological samples will be stored in a network of 28 participating Biological Resource Centers. For blood, a dried blood spot as well as 20 aliquots of blood (2 ml) will be stored for each child: 8 total blood aliquots (EDTA), 4 plasma aliquots (EDTA), 4 buffy-coat aliquots (EDTA), and 4 serum aliquots (Dry SST). Five aliquots for urine, 1 for CSF and 3 for feces will be kept. A lock of hair and 2 feces bottlebrushes will be additionally stored. Standardized procedures for biological sample collection will be used, including standardized blood sampling, transport from each site to the central laboratory (< 24 h), aliquoting in cryotubes, and storage temperature (ambient temperature, -80°C or -196°C depending on the nature of the biological sample). For timely follow-up of collected biological samples as well as their availability, a central database will be created.

Linkage with secondary sources of data

The completion of a death certificate by a physician is compulsory in France on the occurrence of death. Data from this certificate are gathered by the French registry of death

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causes (CépiDc) for the whole French population, by gender, age, country of birth and underlying cause of death coded according to the International Classification of Diseases, 10th Revision (ICD-10). Legal authorization was obtained from CépiDc to gather information concerning all deaths in children less than 2 years old for calculating the exhaustiveness of inclusions in the French SUID registry.

Similarly, health related information concerning infants and their mothers will be gathered as of 2018 in the French SUID registry from the French national health insurance information system (Système national d'information inter-régimes de l'Assurance maladie, SNIIR-AM) and the French hospital discharge database (Programme de Médicalisation des Systèmes d'Information, PMSI). SNIIR-AM covers the entire French population (65.3 million inhabitants) and contains exhaustive data on all reimbursements for health-related expenditures [9,10] including medicinal products such as drugs and outpatient medical and nursing care prescribed or performed by healthcare professionals. PMSI provides detailed medical information on all admissions to French public and private hospitals, including dates of hospital admission and hospital discharge, discharge diagnosis ICD-10 codes, and medical procedures during the hospital stay. Data in PMSI and SNIIR-AM were recently made publically available for epidemiological pharmacological and epidemiological studies [11,12].

To allow for case–control studies to identify risk factors for SUID, data access will be requested in a near future from the Étude longitudinale française depuis l'enfance (ELFE) cohort to use included participants as a control group. ELFE was initiated in 2011 and is a nationally representative cohort of 20,000 children followed from birth to adulthood by use of a multidisciplinary approach to thoroughly characterize the relation between environmental exposures and the socioeconomic context on health and behaviors [13].

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Population data needed to calculate incidence rates as well as socio-environmental information concerning the place of residence/death will also be gathered from the French National Institute of Statistics and Economic Studies [14].

DATA MANAGEMENT AND DATA ANALYSIS

This multicenter registry relies on a Web-based system with data being entered into a central database. The system provides security with protected access and complies with French safety policy [15]. Data entry and validation is performed as a continuous process. For each SUID case, data extracted from MICU and SUID referral center records (approximatively 300 variables) are entered directly online by the medical team in charge of the case. A national project manager continuously controls data completeness and validity and notifies the local medical team in case of discrepancies or incomplete data. Routine permanent quality controls, based on regular on-site inspections, are planned, including training of personnel, compliance with study procedures as well as control of data completeness and validity. Automatic data quality controls are performed periodically to control for missing data and value ranges. Once data from the CépiDc will be available, recorded data will be compared with those from death certificates to estimate the exhaustiveness of the inclusions in the database. Finally, linkages with previously described secondary data sources will be planned once a year.

In this registry, the number of SUID cases occurring in the French territory per year will determine the recruitment size. On the basis of the referral centers' experience as well as the last national estimation performed in 2014 by the French registry of death causes [16], we expect to recruit at least 300 SUID cases each year. A final sample size of about 3000 cases is thus expected for a study period of 10 years.

Confidence intervals, means, standard deviations and frequency distributions will be calculated for all measures. Available data for cases with parental refusals and without a

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SUID referral center in charge will be compared with cases with a SUID referral center in charge. Survival analyses will be used to analyze time-to-event data such as death to identify factors associated with early or late SUID. Multivariable binomial regressions will be used to compare subgroups of SUID children or control children. Multilevel multivariate statistical modeling will also be used to simultaneously study individual and higher-level predictors of outcomes (such as place of residence characteristics). To counteract the potential problem of multiple comparisons, adjustment for statistical significance will be performed when needed. Depending on data and the statistical power available, various other statistical models will also be implemented.

ETHICS AND DISSIMINATION

The registry was registered by the French data protection authority in clinical research (Commission Nationale de l'Informatique et des Libertés, CNIL; no. 915273) and approved by an ethics committee (Groupe Nantais d'Ethique dans le Domaine de la Santé, no. 2015-01-27). This project is based on a network that includes the French non-governmental national association of referral centers for SUID (Association Nationale des Centres Référents de la Mort Inattendue du Nourrisson, ANCReMIN), 34 governmental French medical referral centers in charge of the dead children and their families, Nantes University Hospital, the Nantes clinical investigation center (CIC 1413) and the Sorbonne Paris Cité center of research in epidemiology and statistics (UMR-1153). All these partners are represented in a steering committee responsible for the organization of the registry. A coordination unit is in charge to effectively manage the registry and to implement recommendations from the steering committee. Similarly, a scientific committee was created. This committee is responsible for validating all scientific projects from the registry. Data are available for analysis after validation by the scientific committee according to a validated chart of data access. Interested

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researchers have to comply with the French legislation (i.e., apply for authorization from the CNIL for treatment of personal health data). Research projects have also to be approved by an independent ethics committee. Scientific use of health insurance claims data requires individual accreditation from the data owner, the French national health insurance.

Results will be discussed with associations of families affected by SUID, caregivers, funders of the registry, medical societies and researchers and will be submitted to international peer-reviewed journals and presented at international conferences.

DISCUSSION

The systematic collection of a large variety of socio-environmental, behavioral, clinical, imaging and autopsy data simultaneously with biological samples and administrative data concerning both the children and their mothers appeared critical to study or sustainably prevent SUID deaths in the post "back-to-sleep" era. To our knowledge, this is the first prospective registry specifically designed to respond to this issue even if large population-based registries with less variety of collected data already exist in other countries [17,18]. Because collaboration with such countries is imperative to share best practices, monitor progress, and achieve statistical power for future investigations [5], the OMIN involves as far as possible standardized data to facilitate international collaborations such as meta-analyses or original or replication studies.

To be fully operational and to respond to its objectives, the registry will have to manage several challenges. The first will be to recruit a control population simultaneously with SUID cases for risk-factor studies. Indeed, although the already existing ELFE cohort is a potential way to recruit control children, several exposures are lacking in this cohort and the risk of biased selections may not be ascertained from this data source. The second challenge is to ensure the exhaustiveness of including all SUID cases occurring in the French territory.

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Two French referral centers currently do not participate in the OMIN. Also, preliminary tests seem to indicate a possible under-inclusion in several participating centers. Data from the French registry of death causes, when available, will help better quantify the magnitude of this potential bias and implement corrective measures. The third challenge will be to sustainably maintain both the mobilization of all medical and health actors and caregivers as well as public and private funding, which are essential elements for the success of this project.

In the short-term, this registry has the potential to provide an effective response to the SUID major public health issue by identifying underlying mechanisms that can be prevented and by sharing high-quality data to inform best practices and the accurate classification of SUID deaths. At the same time, such results will help in mobilizing program planners and policy makers and in designing targeted strategies to effectively reduce preventable infant deaths.

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AUTHORS' CONTRIBUTIONS

Dr Karine Levieux conceptualized and designed the study and wrote the initial draft of this article.

Matthieu Hanf conceptualized and designed the study and wrote the initial draft of this article with Dr K. Levieux.

Pr Hugues Patural, Dr Elisabeth Briand Huchet, Dr Inge Harrewijn, Sophie de Visme, Dr Géraldine Gallot, Pr Martin Chalumeau, Pr Christèle Gras-Le Guen and the OMIN study group helped in the conceptualization and design of the study and critically reviewed this article.

Pr Christèle Gras-Le Guen is the guarantor of this article.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Alpes (Saint-Etienne, Lyon, Grenoble), Réunion (Saint-Denis), Antilles-Guyane (Fort-de-France), Saint Brieuc, Tarbes-Vic Bigorre, Corbeil-Essonnes, Bondy, Pontoise, Orléans.

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COMPETING INTEREST

All authors have no conflicts of interest to disclose.

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Figure 1: Localization of the 34 referral centers participating in the French SUID registry

Figure 2: Sudden unexpected infant death management in France and data collection in the French SUID registry

MICU: mobile intensive care unit; ELFE, Étude longitudinale française depuis l'enfance

Figure 3: Timeline and sources of data collection in the French SUID registry

SNIIR-AM: French national health insurance information system; PMSI: French hospital discharge database; CépiDC: French registry of death causes ; MICU: mobile intensive care unit; INSEE : National Institute of Statistics and Economic Studies

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Table 1: Data collected in the French SUID registry

Collected data	Data sources			
	MICU	Referral center	Forensic institute	Others
Social and demographic conditions				
Date and place of birth (child)	X	X		
Gender (child)	X			
Nationality (child and parents)		X		
Ethnicity (child and parents)		X		
Age (child and parents)		X		
Educational level (parents)		X		
Employment status (parents)		X		
Marital status (parents)		X		
Socioeconomic level (parents)		X		
Household composition		X		
Type of social security benefits (parents)		X		
Residency address	X			
Personal and family medical history				
Multiple birth		X		
Gestational age		X		
Birth weight		X		
Small for gestational age		X		
APGAR score at 10 min		X		
Other personal significant events during the perinatal period and early infancy		X		
History of SUID and other sudden deaths in the family		X		
Consanguinity between parents		X		
Vaccination history		X		
Significant medical events in the 72h preceding the death		X		
Significant medications in the 72h preceding the death		X		
Antenatal and current parental behaviors				
Smoking		X		
Alcohol consumption		X		
Other drug consumption		X		
Infant feeding				
Breastfeeding		X		
Last meal before death	X			
Death scene				
Date and time of death	X			
Place of death (address)	X			
Time of last contact	X			
Time of discovery	X			
Arrival time of MICU	X			
Usual and death sleep environment				
Sleep place	X			
Type of surface	X			
Sleep position last placed/found	X			
Head position	X			
Presence and type of objects on the sleep surface	X			

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Collected data	Data sources			
	MICU	Referral center	Forensic institute	Others
Thumb and pacifier use	X			
Room heat	X			
Infant dressing	X			
Room sharing	X			
Nature and results of clinical examinations				
Skin appearance	X	X	X	
Body temperature	X	X	X	
Weight	X	X	X	
Length	X	X	X	
Resuscitation maneuvers	X	X		
Signs of autonomic dysfunction	X	X	X	
Blood chemistry		X	X	
Hematology tests		X	X	
Lumbar puncture		X	X	
Microbiology		X	X	
Eye fundi		X	X	
Imagery investigations (CT scan, MRI)		X	X	
Autopsy		X	X	
Classification of SUID cases by the medical team (Fleming)		X		
Biological samples				
Blood, hair, urine, feces, and cerebrospinal fluid		X		
Other data				
History of health claim reimbursements (child and mother)				X
History of hospital admissions (child and mother)				X
Death certificate information				X
Geocoding of the residency/death address				X
Urbanicity of residency/death address				X
Deprivation index of residency/death address				X
Altitude of residency/death address				X

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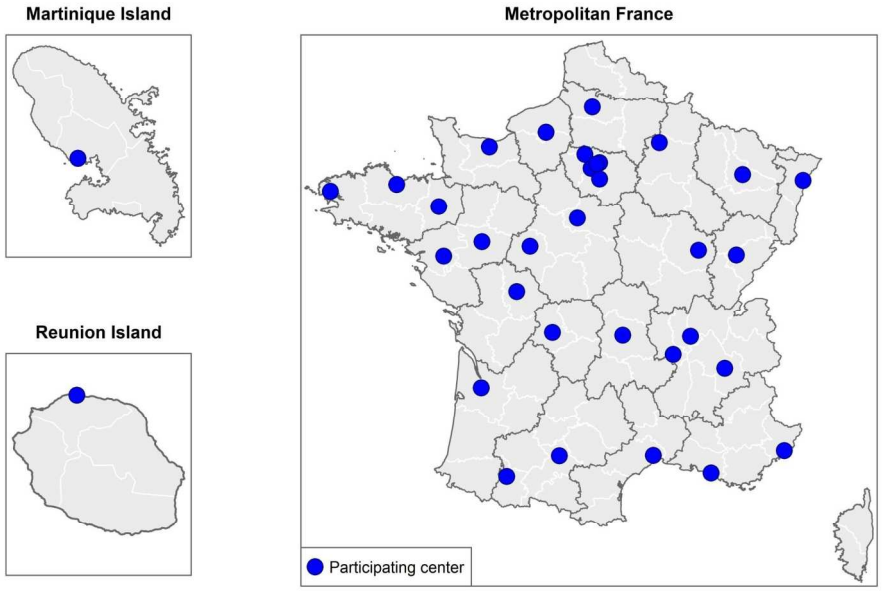

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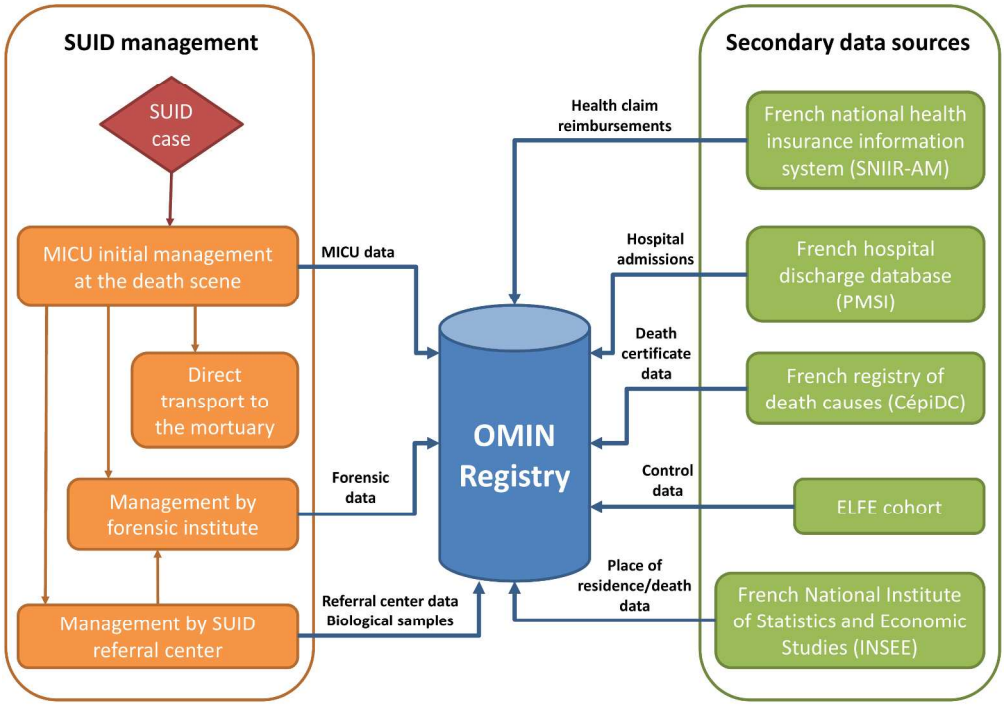

MICU: mobile intensive care unit; ELFE, Étude longitudinale française depuis l'enfance

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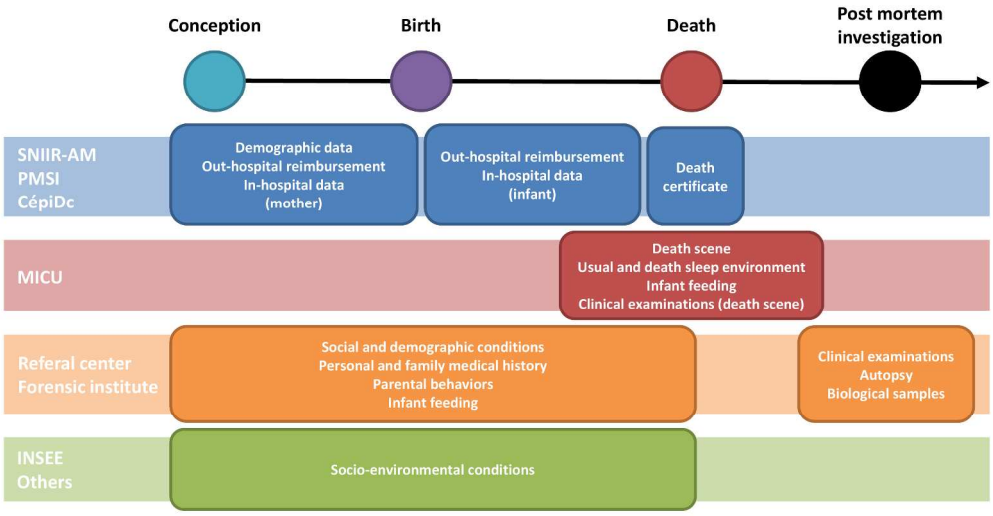

Figure 3: Timeline and sources of data collection in the French SUID registry

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Note d'information pour la participation à la recherche
« Observatoire Morts Inattendues du nourrisson et biocollection»

Titre abrégé : OMIN

Médecin Coordonnateur de l'Observatoire

Nom : LEVIEUX Karine

Service : Urgences pédiatriques

Adresse : Hôpital Mère Enfant 9 Quai Moncousu 44093 Nantes Cedex

Téléphone : 02 40 08 38 06

Courriel : karine.levieux@chu-nantes.fr

Responsable de la recherche

Nom : CHU de Nantes

Adresse : 5, allée de l'île Gloriette, 44093 NANTES

Principaux contacts : Secrétariat Bureau recherche

Téléphone : 02 53 48 28 35 (secrétariat bureau recherche)

Ce document est remis au représentant du patient

Un exemplaire est conservé dans le dossier médical

Madame, Monsieur,

Nous savons à quel point la perte de votre enfant est douloureuse et c'est dans ce contexte difficile que nous souhaitons vous présenter notre projet.

A ce jour en France, il existe trop peu de données disponibles concernant la Mort Inattendue du Nourrisson (MIN). L'Association Nationale des Centres Référents de la Mort Inattendue du Nourrisson (ANCReMIN) a donc décidé de créer en 2014 un Observatoire national (OMIN) pour regrouper l'ensemble des familles concernées par ces décès. Cet observatoire a pour objet principal de collecter des données épidémiologiques fiables, nationales, précises et actualisées dans ce domaine. Il soutient également la réalisation de protocoles de recherches scientifiques visant à explorer les causes possibles des décès et à repérer les facteurs de risques potentiellement évitables et proposer de nouveaux messages de prévention.

Vous êtes bien entendu libre d'accepter ou de refuser de participer à l'observatoire qui vous est présenté. Si vous acceptez, vous resterez à tout moment libre de changer d'avis sans avoir à

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vous justifier. Si vous refusez de participer, les données concernant votre enfant ne seront pas utilisées pour cet observatoire et resteront strictement destinées à un usage médical.

Si vous acceptez de participer, le médecin qui a pris en charge votre enfant collectera les informations nécessaires pour l'observatoire. Ces informations seront recueillies sur la Plateforme d'Echange entre les Professionnels de Santé « PEPS », plateforme internet nationale et sécurisée.

Les données nominatives recueillies afin de permettre la saisie ultérieure des résultats d'examens et seront anonymisées dans le cadre de recherches cliniques ou épidémiologiques. Vos coordonnées (ville et code postal du lieu d'habitation) seront également colligées : seuls les professionnels de santé qui ont pris en charge votre enfant auront accès à ces informations sous la responsabilité du médecin coordonnateur de l'OMIN.

En plus des données médicales de votre enfant, certaines informations concernant vos habitudes de vie, votre niveau socio-économique, votre origine ethnique et des pathologies maternelles pourront être demandées et colligées.

En complément, et afin d'être le plus exhaustif possible, nous souhaitons aussi recueillir des informations auprès des Caisses d'Assurance Maladie concernant les traitements, les hospitalisations, les soins et les médicaments reçus par la maman pendant la grossesse et par votre enfant. Ces données pourraient par exemple nous permettre d'étudier l'impact de la prise de certains traitements médicamenteux dans la survenue des Morts Inattendues du Nourrisson. Sous réserve de votre accord, ces données pourront être transférées à l'équipe OMIN dans le plus strict respect des règles de confidentialité.

Lors de l'examen médical de votre enfant, des échantillons de produits biologiques sont également recueillis (sang, urine, cheveux, liquide céphalo-rachidien et selles). Au moment du recueil, ces échantillons sont 'anonymisés' (codés de façon à ne fournir aucune indication sur votre identité) puis conservés dans un 'centre de ressources biologiques' (ou banque de collections biologiques) en vue de réaliser des dosages. Ces échantillons pourront, par exemple, être utilisés pour mesurer la présence de polluants de l'environnement, de nutriments ou d'agents infectieux. La finalité de ces analyses est de mieux comprendre l'impact de l'exposition à certains facteurs sur la survenue du décès des enfants, dans le but d'améliorer la prévention sur les Morts Inattendues du Nourrisson.

Il faut noter que les dosages réalisés dans le cadre de l'OMIN sont effectués en complément de ceux nécessaires au bilan clinique. Ces résultats ne sont pas communiqués à l'exception de ceux qui sont informatifs pour votre propre santé ou celle de vos enfants ou futurs enfants et qui peuvent donner lieu à un diagnostic et une prise en charge médicale particulière.

Les échantillons biologiques (notamment le sang) permettent de récupérer un échantillon d'ADN (matériel génétique) qui sera conservé, également après anonymisation, en vue de réaliser ultérieurement des analyses génétiques. Ces analyses génétiques auront pour seul but de rechercher des variations spécifiques au niveau de certains gènes qui pourraient être des facteurs de prédisposition à la Mort Inattendue du Nourrisson.

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Pour ce recueil d'échantillons biologiques, un formulaire spécifique d'information et de recueil de consentement vous est présenté en parallèle du présent document. Vous êtes également libre d'accepter de participer ou non à cette biocollection comme au recueil des autres données recueillies dans le cadre de l'OMIN.

Conformément à la loi, vous disposez à tout moment, et par l'intermédiaire du médecin de votre enfant, d'un droit d'accès, d'opposition et de rectification des données enregistrées sur informatique..

Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées et d'être traitées dans le cadre de cette recherche. Vous pouvez exercer vos droits d'accès et de rectification auprès du Docteur mentionné au début de ce document quand vous le souhaitez.

Cet Observatoire a reçu une autorisation de la Commission Nationale Informatique et Libertés (CNIL).

Cet Observatoire ainsi que le présent document ont été présentés au Groupe Nantais d'éthique dans le domaine de la Santé GNEDS.

Le médecin qui vous a proposé la participation à l'OMIN et qui vous a donné oralement toutes les informations nécessaires peut répondre à toutes vos questions.

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A compléter par les titulaires de l'autorité parentale	
Je soussignée : Prénom/Nom : …… …… …… mère de l'enfant (ou représentant légal), accepte : • que mes données nominatives et celles de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** • que les données démographiques, médicales, et paramédicales de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** Date : ……./……/……. Signature :	Je soussigné : Prénom/Nom : …….. …… …… père de l'enfant (ou représentant légal), accepte : • que mes données nominatives et celles de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** • que les données démographiques, médicales, et paramédicales de mon enfant soient recueillies pour cet observatoire : □ **oui** □ **non** Date : ……./……/……. Signature :
Je soussigné(e) le Docteur ou Professeur : Prénom/Nom : …… Avoir informé ce jour les parents de l'enfant (Prénom/Nom) : …… sur l'Observatoire sur la Mort Inattendue du Nourrisson, d'avoir répondu à toutes leurs questions et d'avoir recueilli leur consentement libre et éclairé. Date : ……./……/……. Signature :	

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Merci de conserver l'original du consentement signé et d'en donner une copie aux parents

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