PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The French prospective multi-site registry on sudden unexpected infant death (OMIN): rationale and study protocol
AUTHORS	LEVIEUX, Karine; Patural, Hugues; harrewijn, Inge; Briand Huchet, Elisabeth; De Visme, Sophie; Gallot, Geraldine; Chalumeau, Martin; Gras Le Guen, Christele; Hanf, Matthieu; OMIN, study group

VERSION 1 – REVIEW

REVIEWER	Bo Gregers Winkel Rigshospitalet, Denmark
REVIEW RETURNED	17-Dec-2017

GENERAL COMMENTS	Will you still register deaths on those that choose not to participate? What are the inclusion years?

REVIEWER	Catherine Ellis Coventry University, United Kingdom
REVIEW RETURNED	29-Dec-2017

GENERAL COMMENTS	Reviewer Comments: Overall, the objectives of the proposal are clear and align with internationally identified research priorities; the global requirement to collect standardised data using national databases are essential to understanding the epidemiology of rare conditions such as SUID. This protocol is valuable to other countries and research groups, so of international relevance and relevant to the readership of BMJ open. I would therefore recommend publication of the protocol however, it would be helpful for the authors to provide some clarification on a number of points outlined below prior to publication: Point 2: The starting point of the research needs clarification, a diagrammatic timeline and outline of each data source and their contribution might be helpful to include. More detail is required in relation to notification and inclusion/exclusion criteria, and the abstract refers to both sudden unexpected deaths and sudden unexplained deaths – greater clarification is also needed here. Point 4: Exact replication of the proposed study would have to take account of relevant national factors but the principles of the proposal are replicable and important to publish. Point 5: I have some concerns regarding the proposed requirement for consent from

	'both' parents, this needs to be clarified to include single parent families. This issue may be problematic and impact on the data collection. I also have concerns about using data when one parent does not consent. Further clarification of how these issues will be managed would be useful to publish. Point 7: Multiple imputation may be problematic. Clarification on the use of imputation would be useful, but as the study will be prospective, a missing data strategy may be useful to include

VERSION 1 – AUTHOR RESPONSE

Dear editor,

We thank the reviewers for their useful suggestions that improve the manuscript. Please find listed below a point by point response.

 # Reviewer 1 Comments

Point 1: Will you still register deaths on those that choose not to participate?

SUID cases for which persons who have parental authority choose not to participated where indeed included in the registry to assure the completeness needed for a registry. However, only a minimal set of totally anonymous data (reason for refusal, gender and age at death) is recorded for these SUID cases. *To do so, ethic and regulatory authorizations were specifically obtained.*

To better explain this point the following sentence:

"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."

was changed into:

"To ensure completeness in the registry, SUID cases for which at least one of the persons who have 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)"

Point 2: What are the inclusion years?

The OMIN registry has an open design and aim to include during a period of at least 10 years all SUID cases occurring in France. This registry began inclusions in March 2015. Inclusion will thus be performed at least from 2015 to 2025.

To better reflect this point the following sentence:

"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)."

was changed into:

"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)."

 # Reviewer 2 Comments

Point 1: Overall, the objectives of the proposal are clear and align with internationally identified research priorities; the global requirement to collect standardised data using national databases are essential to understanding the epidemiology of rare conditions such as SUID. This protocol is valuable to other countries and research groups, so of international relevance and relevant to the readership of BMJ open. I would therefore recommend publication of the protocol however, it would

be helpful for the authors to provide some clarification on a number of points outlined below prior to publication

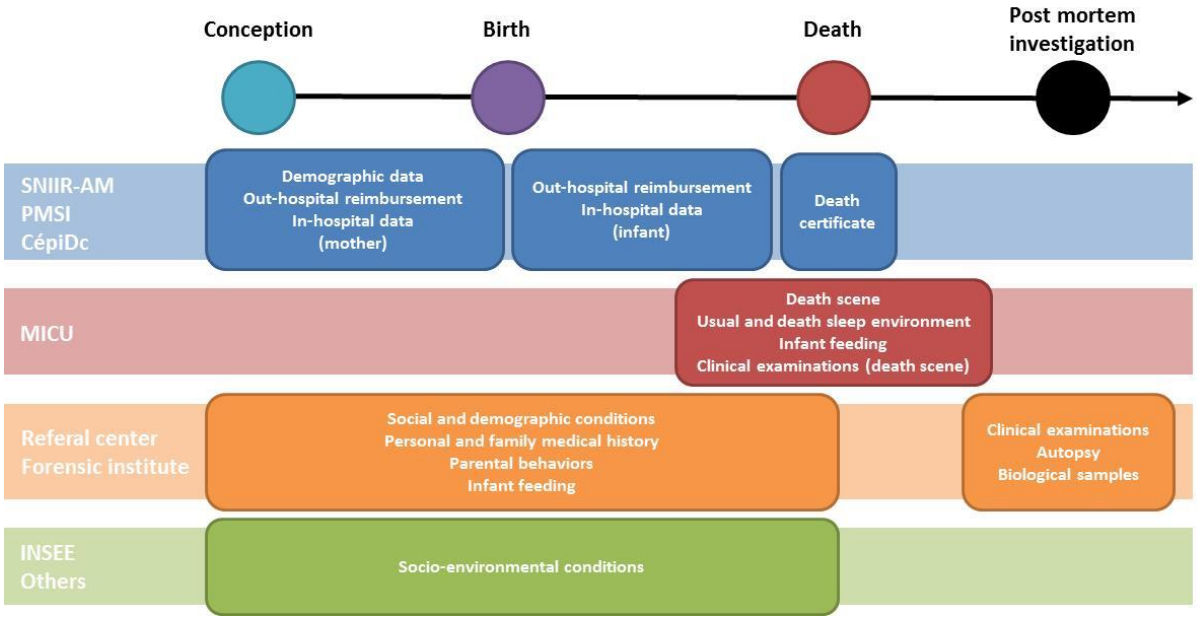
***We totally agree with the reviewer that there is clearly an urgent need* to collect standardized data using national databases to better understand the epidemiology of SUID.**

Point 2: The starting point of the research needs clarification, a diagrammatic timeline and outline of each data source and their contribution might be helpful to include. More detail is required in relation to notification and inclusion/exclusion criteria, and the abstract refers to both sudden unexpected deaths and sudden unexplained deaths – greater clarification is also needed here.

As suggested by the reviewer we added a new figure in our manuscript to better clarify the starting point of the research, the timeline as well as better outline each data source and their contribution.

Here is a description of this new figure:

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



***In the OMIN registry only two inclusions criteria, as defined by the French national health authority, were used: 1) a sudden unexpected death 2) an age at death inferior to 2 years. To collect all the necessary data, a written inform consent from all the persons who have parental authority (often one or both parents) is however necessary. As explained below, SUID cases for which at least one of the persons who have parental authority refuses to participate in the registry are also recorded with a minimal set of totally anonymous data (reason for refusal, gender and age at death)". To better emphasized this point* the following sentences:**

"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."

were changed into:

"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 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 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)"

Finally, we totally agree with the reviewer concerning the use of both sudden unexpected deaths and sudden unexplained deaths. We modify the manuscript in view to only use the official term "sudden unexpected infant deaths".

Point 3: Exact replication of the proposed study would have to take account of relevant national factors but the principles of the proposal are replicable and important to publish.

We totally agree with the reviewer

Point 4: I have some concerns regarding the proposed requirement for consent from 'both' parents, this needs to be clarified to include single parent families. This issue may be problematic and impact on the data collection. I also have concerns about using data when one parent does not consent. Further clarification of how these issues will be managed would be useful to publish.

We totally agree with the reviewer. To better explain this point we totally reformulated our dedicated sentences into:

"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 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 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)"

Additionally, as explained below, SUID cases for which at least one of the persons who have parental authority refuses to participate in the registry are also recorded with a minimal set of totally anonymous data (reason for refusal, gender and age at death) to ensure the completeness of the registry. To do so, ethic and regulatory authorizations were specifically obtained.

Point 7: Multiple imputation may be problematic. Clarification on the use of imputation would be useful, but as the study will be prospective, a missing data strategy may be useful to include.

We agree with the reviewer. A large paragraph dedicated to missing data strategy in the "data management and analysis section" section was already present:

"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."

The choice to not modify these sentences was made.

Concerning multiple imputation, as stated in our "data management and analysis section", because the hypothesis that missing values are missing at random is plausible only for children taken in charge in a referral center, we aim to use multiple imputation only for these children. However, to better clarify our manuscript, we chose to suppress all the sentences related to multiple imputation. Our justification is that MI will be not applied globally (on all studies) but only from case to case when needed and methodologically sounded.