**Protocol for Tracking Ethical Responses in Short Period Incidence Study of Severe Acute Respiratory Infection**

**SPRINT SARI-EARL**

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# ABBREVIATIONS

EARL Ethical Administrative Regulatory and Logistics

EU European Union

FDA Food and Drug Administration, United States of America

INFACT International Forum of Acute Care Trialists

ISARIC International Severe Acute Respiratory and Emerging Infection Consortium

MS Member State

NIH National Institutes of Health, United States of America

PREPARE Platform for European Preparedness Against (Re-)emerging Epidemics

SPRINT SARI Short Period Incidence Study of Severe Acute Respiratory infection

UCD University College Dublin

WP Work Package

# SPRINT SARI Management Committee

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# SPRINT SARI EARL Working group

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# PREPARE EARL WP 1

|  |  |  |  |
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# BACKGROUND & RATIONALE

## Rationale of the research

It is increasingly recognised that there is a significant chance of a large scale epidemic, either in the form of bioterrorism or natural infectious agent1. Yet concerns continue to exist that the infrastructures, funding and staffing may not be in place to address such a threat to public health at the global level.

The recent Ebola outbreak, (of a relatively non virulent agent) revealed many areas that must be addressed in a more timely fashion should a future epidemic evolve. Conduct of clinical trials proved extremely difficult due to the limited health resources in the countries affected, lack of personnel and limited infrastructure in place. It was a year after the first reported case before large scale trials of vaccines were underway and as a result of delays some of those trials are considered to have little chance of being completed because cases are now too rare2. Reasons for delay in clinical trials during the recent Ebola outbreak cited included logistic and ethical problems, such as approval of studies by large regulatory bodies such as the FDA and difficulty recruiting adequate numbers of participants2.

The benefits of large multinational clinical trials include greater generalizability and more rapid results. They allow for more rapid recruitment of greater numbers of participants. However, multinational clinical trials are increasingly difficult to carry out in Europe and beyond due to varying clinical trial regulations and data protection laws, lack of uniformity in application procedures and variation in time frames for approval processes3. Revision of key legislation in both these areas is underway3 but experience has highlighted both in Europe and elsewhere that new legislation can introduce unintended consequences, which may inhibit the effective conduct of research.

For example, in Russia new laws have been introduced which forbid the ethics councils from directly contacting companies, so they cannot request that small errors are corrected – as a result it has been estimated that the ministry's Ethics Council rejects more than 30% of applications to run trials, mostly as a result of administrative or clerical errors in the applications4.

Similarly in India following concerns raised in the Supreme Court about allegations of unethical practices and deaths linked to trials5, new stringent regulations were introduced in an attempt to tighten patient protection. The new law has led to the NIH putting on hold many clinical trials due to concerns that the “law was vague and open to interpretation”. For example, there is confusion as to whether trial sponsors are required to provide medical care for trial participants for the rest of their lives, regardless of whether the trial itself had caused a medical problem. It also seems that patients who received placebos, or for whom the drug did not work, would be entitled to compensation. Additionally, a requirement was enforced to make a videotape of each trial participant giving informed consent for a vaccine trial that could mean video­taping thousands of patients6.

The PREPARE EARL WP recently conducted research that identified a number of issues that significantly delay the current timely conduct of trials (e.g. the agreement of contracts between sponsor and sites)3. However, to date there have only been *a limited* number *of attempts* to understand the time lines of *these approval processes* in EU member states and understand or identify any additional barriers that may exist9.

In this study, we will aim to track these issues thoroughly through both reviewing timelines in applications for a global observational study (SPRINT SARI) for review under the current national legislation in each participating country. Specifically, we aim to understand the time taken for EARL approvals in each country and to identify what the factors that determine or may influence the time line of approval process on a global level. This iterative process will allow researchers in ISARIC and outside to streamline applications to optimise the chances for timely approval.

# OBJECTIVES

## Aim

This research project aims to follow and describe the application of SPRINT–SARI for all applicable EARL approvals in each participating region / nation. We will describe the experience of the researcher submitting the applications and the differing responses received and timelines of the committees (i.e. ethics committees) to a single protocol used in SPRINT-SARI that may create barriers to the rapid deployment of future observational studies and clinical trials in the event of a pandemic.

## Hypothesis

There will be significant heterogeneity in the processes, timelines and the barriers to the rapid approval necessary to conduct SPRINT-SARI in different nations.

# STUDY OUTCOME MEASURES

## Primary outcome

To describe the EARL requirements and timelines for approval in SPRINT-SARI.

## Secondary outcomes

* To describe the ethical approval timelines in SPRINT-SARI.
* To describe the barriers to the rapid ethical approval in SPRINT-SARI.
* To describe the heterogeneity in the responses of differing ethical committees to the SPRINT-SARI protocol.
* To describe and consider the additional barriers identified by the application to EARL approval for SPRINT-SARI.
* To identify solution to the EARL barriers for future winter seasons of SPRINT-SARI or future global interventional studies.

# OVERALL STUDY DESIGN

## Study design

This study will use two principal methodologies. Firstly, we will individually track each ethics application submitted by the different SPRINT-SARI investigators. A structured on-line tracking form (appendix 1) will be sent to each network co-ordinators and clinical trial mangers in each network to record dates of various application events and ethics committee responses. Secondly, we will conduct semi-structured interviews with a selection of these network co-ordinators to identify additional EARL barriers (not captured by the tracking tool).

## Study population

This study will include all the SPRINT-SARI clinical network co-ordinators. They will collect information on the timelines and barriers they identify during the approval process being conducted as part of SPRINT-SARI. Furthermore, we will collect and collate the written responses from various approval bodies (i.e. ethical committees).

## Inclusion criteria

Trial mangers and other relevant staff in each SPRINT-SARI network who are directly involved in ethics application process in that country will be contacted to collect data.

## Exclusion criteria

Project staff members who are not directly involved with SPRINT-SARI approval process will not be contacted for the data. All SPRINT-SARI staff will be able to decline to participate. However, all contacted to date have agreed to participate.

# STUDY PROCEDURES

## Methodology: Online EARL tracking tool

A modification of an on-line questionnaire (see appendix 1) that had been designed and trialled by PREPARE EARL WP 1 (see appendix. This has been based principally on the findings of the previous report (EARL WP 1 2014)3, which identified key themes in the delay of approvals in EU member states. This tool was focused around the principal area of ethical approvals and the timeline required to gain approval.

This tracking tool will be sent to the regional network co-ordinators and trial mangers in each participating SPRINT-SARI network to record the time-line of application and EARL approval responses. The on-line questionnaire includes questions on; date of application, date of responses, documents submitted with the application, languages in which documents submitted, contract requirements, problems encountered during the application process, and satisfaction with the application process. This tool will provide a description of the main timelines in approval and also identify additional themes for further exploration.

As the network co-ordinators in each SPRINT-SARI network will oversee the process of site recruitment and start up, we will ask them to complete this on-line tool as they commence application for the relevant approvals.

In addition, we will ask each co-ordinator to keep a diary form the start of the application process of the main times and dates as well as additional barriers identified to assist with the completion of the online tool (and potential semi-structured interviews).

## Methodology: Semi-Structured interviews

After a period of review of the online tracking data and consultation with stakeholders and an updated review of secondary literature, taking into consideration the themes already included in the our previous reports, a series of relevant themes will be developed that could be discussed in depth via a series of semi-structured interviews.

We will conduct a series of telephone interviews of no longer than one-hour with a representative sample (geographical) of clinical trial managers/co-ordinators from each SPRINT-SARI network for in-depth interview who have agreed to be contacted.

Aide memoires will be designed for these telephone interviews. Verbal consent will be obtained for telephone interviews and will be digitally recorded. For the purposes of analytical rigour and to recognize the continuity of responses, each interview will be given a number at the time of interview and included in our transcripts and analysis. However, this may be removed in the final report and peer review publications if it better protects the anonymity of the participants. Furthermore, this will help the interviews to be anonymised from the start to afford protection for the interviewees and thereby enable a more frank discussion.

Participant information sheets and informed consent sheets are available in appendix II, which will be offered prior to the scheduling of the interview.

All data will digitally recorded, password protected and transferred to a secure drive set up at UCD. Data will be then transcribed for analysis.

## Semi-structured interviews rationale

Interviews will be designed to be loosely structured to enable interviewees to respond in their own time, at their own pace, prioritising matters that they deem important11, 12, thereby minimising (structured) a priori influence. The process will be iterative, as the interviewers will follow themes that emerge in the process. This will assist in fostering more nuanced discussion around key themes.

## Analysis

The data will be thematically analysed using NVivo 10 and analysed longhand to establish themes, configurations or outliers that might emerge. The data will then be read independently thus helping to further validate the findings.

The qualitative data will then be triangulated with the online tacking tool and the previous work in our report 2014 and secondary data.

Finally, the findings will be presented to numerous stakeholders for comment and verified as being representative of their experiences and recognized as accurate.

# ETHICS

## Ethical issues of the study: Overview

Ethical issues relate mainly to the anonymisation of respondents and confidentiality of data and its duration of storage. These will be addressed below.

## Ethics Committee approval

Ethical approval for this study has been sought from University College Dublin Human Research Ethics Committee.

## Confidentiality of data: On-line survey

Data will be collected using an on-line questionnaire designed using the open source survey application *LimeSurvey* installed on the secure servers of Ireland's National Research & Education Network (HEAnet). All data collected will be saved on these servers and only survey administrators will have access to this. Once the survey is completed, data will be exported from these servers and saved as password protected Excel files on secure UCD drives. This data will not be shared. No individual ethics committees will be identified and analysis will be carried out only at the country level. Identity of the respondents will be kept confidential and will not be usedduring any analysis. Collected data will be stored for 5 years.

## Consent: On-line survey

All networks in SPRUNT-SARI have already agreed to participate. However, each national co-ordinator will have the option not to collect the relevant data for their nation if they object. Completion of the survey will include a section for consent.

## Confidentiality of data: Semi-structured interviews

Audio recordings of interviews will be encrypted with a password and saved on a secure drive. These audio recordings will be destroyed once transcripts of the recordings are secured and stored. These data will be de-identified and the interviews will be anonymised to protect the privacy and confidentiality of the interviewees.

## Consent: Semi-structured interviews

A question is being asked on the on-line survey (where identified) to provide contact details (optional) of respondents who are interested to participate in the subsequent qualitative interview. Those who express interest in participating and have collated a diary will be contacted for interview and verbal consent will be sought before the interview date is arranged.

# DATA MANAGEMENT

## Data collection methods

Data on each ethics application submitted by each SPRINT-SARI network will be collected from project managers or any other relevant staff member directly involved in the application process. These data will be collected via a diary and then submitted centrally through a structured on-line questionnaire send to project managers in each country. The diary will have a semi-structured format to allow the collation of EARL barriers under different headings (i.e. ethical, logistic etc.) to facilitate data collection, processing and the later interviews.

## Data variables collected

* Details on ethics committee organisation in their nation
* Date of first ethical application
* Documents required to be submitted
* Languages in which application/protocol submitted
* Date of response from ethics committee
* Outcome of application
* Additional information on local requirements
* Respondents’ opinion and satisfaction/dissatisfaction on application and approval process

## Data management

Data collected through the on-line questionnaire will be saved on the servers of Ireland's National Research & Education Network (HEAnet). Once the survey is completed, these data will be exported from the survey system to Excel format and saved on secured computers as password protected files. Only the research team will have access to this data. Quantitative analysis will be carried out using IBM SPSS Statistics 20.

## Data quality & monitoring

To ensure the data quality various data integrity checks, logical skipping and branching are included in the on-line questionnaire. This is to ensure that only relevant questions will be shown to the respondents based on their previous inputs and thereby ensure data quality.

# STATISTICAL CONSIDERATIONS

We anticipate 15-20 networks will take part with approximately 200-400 individual sites requiring approvals.

## Statistical and analytical plan

Both quantitative and qualitative data analysis methods will be employed to analyse the data. Average time taken for ethical approval will be calculated. Statistical analysis will be carried out to see whether there is significant difference in approval time depends on study design, consent process, ethics committee type or country. Responses from ethics committees will be analysed to see which factors create major hurdles for fast approval of ethics applications.

# RESEARCH TIMELINES

|  |  |
| --- | --- |
| Time frame | Milestone |
| September 2015 | UCD Ethical approval - sought |
| October 2015 | Protocol sned to sits |
| January-March 2016 | Northern hemisphere responses |
| July – October 2016 | Southern hemisphere responses |
| Novermber 2016 | First Report |

# REFERENCES

1. Gates B. The next epidemic- lessons from Ebola. New England Journal of Medicine. 2015;372(15):1381-4.

2. Hayden EC. Ebola teaches tough lessons about rapid research. Nature. 2015;521(7553) :405–6.

3. PREPARE. First Report: EARL (Ethical, Administrative, Regulatory and Logistical) Solutions. Dublin: University College Dublin, 2014.

4. Katsnelson A. Russian drug law hinders clinical trials. Nature. 2012;481(7381):250.

5. Cressey D. India shakes up rules on clinical trials. Nature. 2012:<http://www.nature.com/news/india-shakes-up-rules-on-clinical-trials-1.11223>.

6. Reardon S. NIH makes wary return to India. Nature. 2014;506(7487):143 - 4.

7. Council of the European Union. Proposal for a regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (general data protection regulation)2015. Available from: <http://data.consilium.europa.eu/doc/document/ST-9565-2015-INIT/en/pdf>.

8. European Parliament and Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union [Internet]. 2014; (L 158):[1-76 pp.]. Available from: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_158_R_0001&from=ES>.

9. Hearnshaw H. Comparison of requirements of research ethics committees in 11 European countries for a non-invasive interventional study. BmJ. 2004;328(7432):140-1.

10. European Parliament and Council of the European Union. Directive 2001/20/EC of the European parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal [Internet]. 2001; (L 121):[34-44 pp.]. Available from: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32001L0020>.

11. Flick U. An introduction to qualitative research. London: Sage; 2006.

12. Kvale SBS. Interviews : learning the craft of qualitative research interviewing. Los Angeles: Sage Publications; 2009.

# APPENDIX

## Appendix 1: Online Tracking Tool

Please follow the link to see the most recent version of the ethics tracking tool

<http://prepare.ucd.ie/surveys/index.php/945543>

(Double click the below image to open a PDF version)



## Appendix 2: Participant Information Sheet for Telephone Interviews

Tracking Ethical Responses in Short Period Incidence Study of Severe Acute Respiratory Infection SPRINT SARI-EARL

**Why is the research needed?**

SPRINT-SARI EARL aims to identify barriers to setting up and conducting research during a pandemic/epidemic and includes consideration of any social and cultural values.

This aims to better inform ISARCI / INFACT of current practices and problems arising in different countries when conducting observational studies and clinical trials during future pandemics.

As part of this exercise we are conducting primary and secondary research. The primary research data will be collected via qualitative interviews and via an online EARL approvals tracking tool.

The timeline is short and we wish to involve people with relevant experience at this early stage of the project to tap into your experience.

**Who is undertaking the research?**

This researh is being lead by Prof A Nichol on behalf of the SPRINT SARI EARL investigators.

**About the fieldwork**

We also wish to undertake a small number of telephone interviews to follow up on the experience in submitting the EARL approval in SPRINT-SARI. This will enable us to gather more supplementary information and to add rigour to our analysis.

**Why have I been approached to take part?**

Your name was suggested to us by the lead of your network, as a colleague who has assisted with EARL approvals.

**What will I be asked to do if I take part?**

You will be asked to consent to a telephone interview of approximately 45 minutes. A date will be set at your convenience in the very near future.

The interviewer will ask a range of questions about your experiences in relation to Ethical, Administrative, Regulatory and Logical barriers and potential solutions identified when submitting for approvals in your region.

**Do I have to take part?**

Participation is completely voluntary and there is no pressure on you to take part. You are welcome to change your mind at any time before the interview even if you have already said that you want to take part in this study. You can also change your mind and pull out during the interview at any time. If you decide that you want to withdraw the information you have provided after the interview then we can do this if you contact us before we have started analysing it. This will be 2-3 weeks after the date of the interview.

**Can I be identified by taking part?**

The information you provide and any published data will be anonymous. The data collected for this study will be coded and recorded with your name removed. All recordings will be destroyed following transcription and stored securely and only the researchers conducting this study will have access to this data. Interview data will be kept in a locked cabinet or will be stored securely (e.g. on a secure drive on password protected computers). With your consent, the results of your interview may be archived by University College Dublin for potential use by other researchers in the future but this will only take place if all the features that could identify you, other individuals and/or your local areas can be removed so that the transcript is completely anonymous. Anonymous direct quotations from your interview may be used in the reports or publications from the study but your name will not be attached to them.

**What will happen to the research findings?**

The results will be analysed and reported to other researchers involved with PREPARE to inform their research work packages and may form part of work to be submitted for publication in an academic or professional journal. If you would like to stay informed about the project please see <http://www.prepare-europe.eu/>

**Who has reviewed the project?**

This study has been reviewed by the UCD Research Ethics and permission gained to proceed.

**What should I do next?**

You will be contacted by a member of the EARL research team, and with your approval, we will arrange a convenient time for the telephone interview to take place. At that time, following an opportunity to ask any questions you may have about the research, you will also be invited to give your consent to taking part by offering verbal consent. Participating in the interview will evidence your continued consent at the time of interview.

**Where can I find out more information if I need to?**

If you have any questions about the study in the first instance please contact:

Prasanth Sukumar

Email: prasanth.sukumar@ucd.ie

Tel: 00353 (1) 716 4646

**Making complaints:**

If you wish to make a complaint or raise concerns about any aspect of this study and do not want to speak to the researchers, you can contact the project lead:

Professor Alistair Nichol

Email: alistair.nichol@ucd.ie

## Appendix 3: Consent Form for Telephone Interviews

Tracking Ethical Responses in Short Period Incidence Study of Severe Acute Respiratory Infection SPRINT SARI-EARL

Please read the participant information sheet and tick each box below if you agree. If you have any questions then please contact the researcher.

1. I confirm that I have read the information sheet and fully understand what is expected of me within this study. ❑Y / ❑N

2. I confirm that I have had the opportunity to ask any questions and to have them answered. ❑Y / ❑N

3. I understand that I am not obliged to take part in this study and that I can withdraw my agreement before or during the interview. I also understand that I can ask for any information I provide during an interview to be withdrawn provided I do this before data analysis begins to be written up (approximately 2-3 weeks after the date of the interview). ❑Y / ❑N

4. I understand that the information from my interview will be combined with other participants’ responses, anonymised and may be used in reports, conferences and journal publications. ❑Y / ❑N

5. I agree for the information that I provide in my interview to be archived by University College Dublin for potential use by other researchers in the future but that this will only take place if all the features that could identify individuals and local areas can be removed. ❑Y / ❑N

6. I consent to the research team keeping my contact details so they may, with this consent, contact me again in the future but that this information will not be passed onto anyone else. ❑Y / ❑N

7. I consent to take part in the above study. ❑Y / ❑N

Name of Participant ……………………………………………..

Date ………………………………

Name of Researcher ……………………………………………..

Date ………………………………