Ebola Data Platform - Data Access Application Form

Please review the Data Access Guidelines and the Data Transfer Agreement* before completing this form. Note that the details of all approved applications will be made publicly available on the Ebola Data Platform website.

Please complete all sections of this form fully and return to ebolaDAC@iddo.org with the following attachments:
- Academic CV of the Lead Requestor (any format)
- Conflict of Interest Forms completed by the Lead Requestor and each of the Co-applicants listed

**SECTION A: RESEARCHER / RESEARCH TEAM INFORMATION**

<table>
<thead>
<tr>
<th>Lead Requestor Details (please attach an academic CV)</th>
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<tbody>
<tr>
<td><strong>Title</strong></td>
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<tr>
<td><strong>First name (given name)</strong></td>
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<tr>
<td><strong>Surname (family name)</strong></td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td><strong>Position at employing organisation/ institution</strong></td>
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<tr>
<td><strong>ORCID ID</strong></td>
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<td><strong>Email</strong></td>
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<tr>
<td><strong>Telephone/Skype/WhatsApp</strong></td>
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</table>

**Employing Organisation/institution**

Institution with a remit including health, research or academic pursuit, and with legal status which includes the scope to sign the Data Transfer Agreement*

<table>
<thead>
<tr>
<th>Institution name</th>
<th>National Public Health Institute of Liberia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Address</strong></td>
<td>Oldest Congo Town</td>
</tr>
<tr>
<td><strong>Department (if applicable)</strong></td>
<td>Division of Infectious Disease and Epidemiology</td>
</tr>
</tbody>
</table>

Please acknowledge that your institution agrees to execute the Data Transfer Agreement (in the case of your application being approved)

| YES |
| (delete as appropriate) |

* The Data Transfer Agreement is a contract between the University of Oxford (on behalf of IDDO) and the recipient institution that governs the legal obligations and restrictions, as well as compliance with applicable laws and regulations, related to the transfer of such data between the parties. The named Institution will be required to sign the data transfer agreement before the release of any data by IDDO.
Co-applicants
(ALL individuals accessing the data must be listed. Any additions must be notified to the Ebola DAC)
Add rows as necessary.
Please attach copies of the Conflict of Interest Form, completed by each of the individuals above.

<table>
<thead>
<tr>
<th>1. Name</th>
<th>Dr. Mahamoud Sama Cherif</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Title</td>
<td>Researcher</td>
</tr>
<tr>
<td>1. Organisation/Institution</td>
<td>Gamal Abdel Nasser University of Conakry</td>
</tr>
<tr>
<td>2. Name</td>
<td>Dr. Kwame Oneill</td>
</tr>
<tr>
<td>2. Title</td>
<td>Researcher</td>
</tr>
<tr>
<td>2. Organisation/Institution</td>
<td>Ministry of Health and Sanitation – Sierra Leone</td>
</tr>
<tr>
<td>3. Name</td>
<td>Prabin Dahal</td>
</tr>
<tr>
<td>3. Title</td>
<td>Post-Doctoral Researcher</td>
</tr>
<tr>
<td>3. Organisation/Institution</td>
<td>IDDO, University of Oxford</td>
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</table>

**SECTION B: RESEARCH PLAN**

<table>
<thead>
<tr>
<th>Title of Proposed Research</th>
<th>Better clinical management strategies that will inform affected countries through understanding of host, viral and supportive care factors associated with mortality</th>
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</thead>
<tbody>
<tr>
<td>Is this a re-submission of a previous application that has been reviewed by the Ebola DAC? If so, please provide the surname of the Lead Requestor and submission date of the previous application.</td>
<td>Yes Yeabah 13/03/2020</td>
</tr>
</tbody>
</table>

**Summary of Research in Lay Language** *(suggested ~ 100 words)*

This research will expand on the existing information on clinical management strategies with focus relating to the host, viral and supportive care factors associated with mortality. Efforts going to be tailored toward survival analysis. Considering the patient parameters, the research analysis will undertake the effort to explore the relationships between changes in parameters and the associated risk of death. During the end of the research, a propensity score matching approach will be used to re-evaluate the association between intervention and mortality to assess possible causal association. Findings from this study will be analysed epidemiologically and disclosed in a formal publication follow by stakeholder’s engagement in the affected countries. This project is supervised by the Chief Scientist of the National Public Health Institute of Liberia, Dr Mosoka Fallah, who is currently the Director General of the Institute.

**Scientific Summary of Research** *(suggested maximum 300 words)*

Yearly, infectious disease outbreaks and epidemics cause significant human, economic and social consequences worldwide. Global trends in travel, deforestation, urbanisation, migration, climate change and population growth fuel the risks of more frequent and larger outbreaks, making the need for countermeasures increasingly urgent. However, limitations in human, technical and financial resources mean that some of the most at-risk countries do not optimally detect and respond to the threat of outbreaks. The tragedy of recent Ebola virus disease (EVD) outbreaks provides an example of these risks. EVD research has been heavily constrained by the lack of accessible and standardised data. As a result, empiric and scientific evidence to inform advances in diagnosis, triage, management and follow-up of suspected and confirmed EVD patients remains inadequate. Therefore, this research project will address EVD research priorities and translate the research outcomes into concrete health policy as well as involving a substantial data management effort that is well coordinated in the countries affected by EVD.

**Summary of Research Objectives** *(suggested maximum 200 words)*
The general aim of this research is to improve the EVD patient management in the context of future outbreaks. The specific objectives are:

1) To identify host, viral and health care factors, including therapeutic interventions, associated with risk and time of death
2) To explore relationships between changes in parameters and subsequent risk of death
3) To re-evaluate the association between intervention and mortality to assess possible causal association

### Primary and Secondary Outcome Measures (suggested maximum 200 words)

The primary outcome is death during hospital stay and time of outcome is defined as time of death or time of discharge for patients who have not died during hospital stay.

### Proposed Methodology and Statistical Analysis Plan (suggested maximum 400 words)

The proposed approach will involve requesting for the available patient records, reviewing the relevant variables that will answer to the objectives and subsequently inform clinical management strategies relative to EVD. Qualitative

A mixed effects logistic regression model (or Cox model) will be fitted. Random intercepts for EVD treatment centres will be included in all models (as frailty terms in Cox regression); and for patients will be included in longitudinal models. Interactions of main risk factors with geographical locations and time during the outbreak will be examined. The variable selection process will be in accordance with the recommendations in the Heinze et al (2018) study.

Statistical analysis will follow PRISMA guidelines for IPD meta-analysis and TRIPOD statement for the development of prediction models. The risk of bias for individual studies will be evaluated at the outcome level assessing: missing data and methodology to evaluate outcomes (if applicable). Internal validation of prediction model will be performed using bootstrapping and cross-validation, estimating overfitting of the developed models and optimism in their predictive performance. Missing data is anticipated and statistically principled approaches of multiple imputation or inverse probability weighting under Missing at Random (MAR) mechanism will be used; sensitivity analysis considering departures from this mechanism will be conducted. All the codes and the details of the fitted models will be made publicly available to facilitate an individual external validation and incorporation into existing diagnostic applications.

Exclusion and inclusion criteria will be set to ensure that records of patients with no RT-PCR results be carefully review prior and during the analysis epoch.

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### Ethics (suggested maximum 300 words)

Provide details of any ethical considerations relating to the research proposal. Additionally, list any approvals required by your institution to undertake this work, list reference numbers of any approved proposals, or explain why no approvals are required.

In mid-2019, approval was considered by the Liberia National Ethic Review Board for the smooth implementation of this project. With the approval from the committee, the National Public Health Institute of Liberia (NPHIL) is set to progress in the project implementation. This approval gives the institute authorization to data access and re-use of patient data collected in the context of a public health emergency for research. As part the responsibility of the NPHIL with respect to ethical integrity during the implementatio of the project, NPHIL along with its co-implementing party, will protect the privacy and interstes of the individual patient record and communities from which these data originated.

Considering the interst of the project objectives, the data to be used will be retrospective anonymized random data which indicates the highest level of confidentiality of patients record to be maintained. The issue around data security amongst others ethical considerations will be
adopted in order to ensure that success of this project is achieved in line with the general data protection regulation on the Ebola Data Platform. This application falls under the Ebola Data Platform protocol and research agenda already approved by the Liberia National Ethics Committee. Dr. Mosoka Fallah made the original application to the ethics committee as a co-investigator for the Ebola Data Platform. He is now co-investigator on the MRC research project that is being implemented under the protocol and research agenda approved in the original ethics application, and he is supervising my work as a co-researcher on this project at the National Public Health Institute of Liberia.

**Publication and Dissemination Plan** *(suggested maximum 300 words)*

*Provide details of plans for authorship/acknowledgement of data contributors.*

*Provide details of timelines for publication and dissemination of research findings.*

The primary purpose of this project is to increase knowledge in the policy, academic and health communities to improve outcomes for patients at risk of EVD and emerging infections and subsequently provide adequate options strategies in clinical management of EVD case patients during response to future outbreak. This activity will produce evidence that inform policy decisions and reinforce the depth and availability of capacity for improved health security.

As a way of ensuring that publication and dissemination are enhanced, a mid-term project meeting will be held in Sierra Leone to carefully review the interim findings of the analysis, beginning with manuscript drafts and finalize dissemination plans which will last for three to four days. Following the mid-term meeting and work done on action points emulating said meeting, a result dissemination session will be held in Liberia to present overall findings and the communication plan. This dissemination session will provide opportunity to share the experiences of the project team with other researchers and public health workers to promote further cross-disciplinary collaboration.

The communication plan will consider the presentation of the results at regional and international scientific conferences and be made available publicly on the Ebola Data Platform website. Manuscript of this effort will be published in infectious disease journal. Furthermore, dissemination will be done through stakeholder-targeted newsletters, electronic bulletins, local radio stations, websites, and social media streams which will include the EVD survivor communities. The results will adequately be translated into the national public health policy.

The Principal Investigators will report all outputs to the Africa CDC, the West African Health Organisation (WAHO) and the WHO Research and Development Blueprint committee for consideration in the next iteration of regional and international policies, including the WHO Ebola/Marburg Research and Development Roadmap.

**Addressing Knowledge Gaps** *(suggested maximum 300 words)*

*Provide details of how this research will address knowledge gaps of importance to those affected by or at risk of emerging and poverty-related diseases.*

The Ebola outbreak of 2013-2016 reinforced the need for collaboration and an integrated approach to the response to an outbreak of such magnitude. Since Ebola appeared in 1976 data and information has been scanty and not well coordinated. This project seeks to address that need by cross referencing different better clinical management strategies that will inform affected countries through understanding of host, viral and supportive care factors associated with mortality data sets and put forward a meaningful option that will influence policy and decision making. There was a paucity of information about best treatment options. The prognostic indicators will help guide treatment protocols for EVD and other viral haemorrhagic fevers. This will go a long way in reducing case fatality rates and mortalities associated with EVD.

The Ebola research has been significantly limited by the inaccessibility and incompatibility of data. Empiric and scientific evidence to inform advances in diagnosis, triage, management and follow-up of suspected and confirmed Ebola patients remains inadequate. This was emphasized by the WHO Ebola/Marburg Research and Development Roadmap that called for the establishment of an interoperable system to enhance capabilities for collecting, reporting, analysing, and sharing
data. The project aims to address the research priorities identified by the Ebola-affected countries and address the capacity needs to those leading national outbreak responses in these countries. This project will create an avenue for the survivor cohort that would explain and be put forward for the improved case fatality and also triangulate the most prevalent complication as sequelae to their infection. Of concern to the survivors is their potential risk to their loved ones. Information on the prevalence of the virus or viral fragment of Ebola has now improved but still not yet optimal. Due to the large quantum of data from the EDP, an attempt will be made to help reform sexual and reproductive health guidelines for survivors.

Collaboratively, the co-applicant’s objectives with alignment to my will contribute to achieving the primary objective and the results from this application would form the basis on which the recommendations will lead to the generation of better health policy for various governmental and non-governmental organizations. This will enhance the collaboration amongst the affected countries in strengthening the cross border surveillance in the region.

The treatment regimen and outcome of the patient in this study will go a long way in informing treatment protocols ad guidelines in Liberia. There has been several controversy on the Use of Intravenous fluids as opposed to oral rehydration on health outcomes of Ebola patient. The huge data sets will help put forward the pros and cons of each type of rehydration.

This application seeks to put forward the effect of three key factors on the outcome of a patient with Ebola. These factors and how they affect the patient are the host, viral and treatment regimen. The interplay of these three factors on outcome of the patient will inform or contribute on how the future of diagnostics and treatment of Viral Haemorrhagic fevers will be in Liberia going forward.

**Equity and Capacity Building** *(suggested maximum 300 words)*

Provide details of how this research will support health equity and/or capacity building in endemic regions affected by or at risk of emerging and poverty-related diseases.

*Please refer to the Ebola Data Platform Approaches to Capacity Building for guidance.*

This research application is made to explore and generate reasonable approaches to improve on emergency preparedness and response with keen treatment for future outbreaks of Ebola Virus Disease. In order to ensure that this endeavour is impactful toward the good of the affected region and beyond, a strong collaborative effort between the National Public Health Institute of Liberia, the Ministry of Health and Sanitation of Sierra Leone, the National Health Security Agency of Guinea, and Oxford University have been initiated to answer critical questions on EVD. More specifically, the approach to evidence generation taken by this project maximises benefits to the communities affected by Ebola. In line with capacity building, the project highly considers the enhancement of local researchers’ skills and competent from the affected countries by being awarded a TDR clinical fellowship for one year located in Oxford to better sharpen their understanding in statistics and data management.

This opportunity provided to the local researchers not merely expose the researchers to better learning environment but rather increase their knowledge and skill in statistical and data management. It will lead to the ability of each researcher from the affected countries to perform advanced analysis, writing appropriate manuscript for publication, and ensuring that the recommendation from this project be incorporated in health policy and plan that have the propensity of imparting the lives of the local population most especially during emergency situation or outbreaks. Interestingly, a component of this project speaks to cascading the similar knowledge in the researcher countries which indicate a trigger down effect of the knowledge and skills that will be acquired by these researchers while in Oxford.

The project partners have prioritised the need to better understand how to balance the strength of clinical management strategies that will inform affected countries through understanding of host, viral and supportive care factors associated with mortality in different contexts for future outbreaks. By leveraging the pooling of the largest individual patient data repository assembled under the EDP, the most conclusive evidence on these research questions can now be generated by this project. This will be used to influence policy on future management of Ebola.
The equitable and sustainable partnership between the various partners is built on collaboration and data sharing to enhance capacity building and training opportunities for a more robust national health security system.

**Funding** *(suggested maximum 100 words)*

Provide details of how this research will be funded/resourced.

This research will be funded through the UK Medical Research Council grant with additional funding secured through the TDR fellowship to provide sustained support regarding compensation of the Researchers, Co-investigators and the Principal Investigator. The logistics for software, housing, traveling cost and review meetings to be held in Conakry, Freetown and Monrovia.

**Scientific Review** *(suggested maximum 200 words)*

Provide details of how the details of the project outlined above have been scientifically reviewed. This could be by your institution, a funder/donor or review committee.

The research priority as outlined in this application is part of the research questions in the Ebola data Platform research agenda. This application was reviewed by Dr Kasia Stepniewska, Head of Statistics at the Infectious Diseases Data Observatory at the University of Oxford.

**SECTION C: DATA**

**Data Variables**

Provide a list of the data variables and data sources required to achieve the research objectives.

Note: Data sources can be listed as populations (e.g. all EVD-positive pregnant women, or all children under 16 years of age from Liberia) or as datasets from a source listed on the Accessing Data web page (these should be named by ‘Contributing organisation, Country, City’ as listed in the table). Get in touch if you have any questions about this ebolaDAC@iddo.org

Based on the case definition given by WHO which was applied in the outbreak of 2013 -2016 which reads: 1) any person, alive or dead, who has (or had) sudden onset of high fever and contact with a suspected, probable, or confirmed EVD case-patient, or a dead or sick animal; or 2) any person with sudden onset of high fever and ≥3 signs/symptoms (headache, generalized or articular pain, intense fatigue, nausea/vomiting, loss of appetite, diarrhoea, abdominal pain, difficulty swallowing, difficulty breathing, hiccups, miscarriage); 3) unexplained bleeding; or 4) sudden unexplained death.

The data variables include but are not limited to the following broad themes:

- Case patient sociodemographic
- Case patient clinical signs and symptoms
- Co-morbidity
- Exposure factors
- Diagnostic profile (laboratory parameters, viral load)
- Travel history
- Case management (treatment, psychosocial, health promotion)
- Epidemiological charateristics
- Pregnancy status
- Patient outcome status (discharged alive or death in hospital)
- Time of outcome status

Specific data variables requested are:

- Name of patient
- Age
- SEX
- History of Fever
The mentioned variables were requested due to the research question that is intended to address prevailing public health problems in relation to Ebola Virus Disease. The datasets to be used in this study will be sourced from the data repository held in the Ebola Data Platform.


