Ebola Data Platform - Data Access Application Form

Please review the Data Access Guidelines and the Data Transfer Agreement[1] 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	
Lead Requestor Details *(please attach an academic CV)* *1) https://www.klinikum.uni-heidelberg.de/heidelberger-institut-fuer-global-health/directorate/members/baernighausen-till* *2) https://www.marsilius-kolleg.uni-heidelberg.de/fellows/baernighausen.html* *3) Biosketch is attached in the email*	
Title	**Professor Dr. Dr.**
First name (given name)	**Till**
Surname (family name)	**Bärnighausen**
Gender	**Male**
Position at employing organisation/ institution	**Director of Institute**
ORCID ID **https://orcid.org/**	https://orcid.org/0000-0002-4182-4212
Email	[redacted]

Telephone/Skype/WhatsApp	[redacted]
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***1	
Institution name	University Hospital Heidelberg
Address	Im Neuenheimer Feld 130.3 69120 Heidelberg
Department (if applicable)	Heidelberg Institute for Global Health (HIGH)
Please acknowledge that your institution agrees to execute the Data Transfer Agreement (in the case of your application being approved)	YES

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.*	
1. Name	Kwame Oneill
1. Title	Dr.
1. Organisation/Institution	Ministry of Health and Sanitation, Sierra Leone
2. Name	Heather Hufstedler

2. Title	none
2. Organisation/Institution	HIGH, University Hospital Heidelberg
3. Name	Lauren Maxwell
3. Title	Dr.
3. Organisation/Institution	HIGH, University Hospital Heidelberg; WHO; Emory University
4. Name	Alexander Danzer
4. Title	Prof. Dr.
4. Organisation/Institution	Katholische Universität Eichstätt-Ingolstadt

SECTION B: RESEARCH PLAN

Title of Proposed Research	What are the determinants of mortality for EVD in Human population?
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.	no

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

The Ebola virus disease is an extremely infectious disease with a high case fatality rate, ranging from 25-90%. There is currently no known treatment that effectively neutralizes the virus. Instead, supportive treatments, such as oral rehydration solutions (ORSs), and interventions, like infection prevention and control and contact tracing, are the most crucial strategies to infection and disease management.

With this application, we are interested in using IDDO's compiled data from the 2014-2016 Ebola outbreak in West Africa to explore the determinants and predictors of mortality in EVD patients. This could include but is not limited to time to diagnosis and treatment; and host, viral and supportive care factors.

Understanding the relationships between these factors could improve clinical management strategies, inform affected countries throughout the region, and improve the likelihood of survival should future outbreaks occur.

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

Review of Ebola (EBV/EBOV)

Ebola virus (EBV or EBOV) is a filovirus discovered in the Democratic Republic of Congo (DRC) in 1976. There are six species of this virus-- Mayinga, Reston, Tai Kikwit, Sudan, and Bundibugyo. The zoonotic potential is well-documented in some and unclear in others, but the seriousness of the disease in humans makes all strains a concern. Recent re-evaluation of studies has led to widespread acknowledgement that the symptoms are variable with decreased emphasis on bleeding as usage of the term 'ebola hemorrhagic fever' in favor of 'ebola virus disease'.

Common transmission pathways include close contact, such as living in the same household with an infected person[1], contact with infectious body fluids[2], contact with cadavers[3]. There is also evidence that men could transmit the virus through sexual contact and that the virus may live in semen for at least 2.5 years[4]. Percutaneous transmission has also been noted[5] There is also the possibility that infection could be subcutaneous. Incubation period is generally 6-10 days, but the timeframe can be as wide as 2-21 days. High case-fatality ratios-- between 60% - 88%[6]-- in countries where this disease is endemic, e.g. Liberia, Sierra Leone, Guinea, means that clear treatment protocols which optimize chances of survival are crucial. One way to do this is to better understand the determinants of and supportive treatments for the disease.

Lack of knowledge surrounding determinants of and supportive treatments for Ebola

Development of EVD in humans is not well understood but has been shown to have some similarities with other causes of viral hemorrhagic fever (VHF) and bacterial

[1] Dean NE, Halloran ME, Yang Y, Longini IM. 2016. Transmissibility and pathogenicity of Ebola virus: a systematic review and meta-analysis of household secondary attack rate and asymptomatic infection. *Clin. Infect. Dis.* 62:1277–86

[2] Dowell SF, Mukunu R, Ksiazek TG, Khan AS, Rollin PE, Peters CJ. 1999. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Épidémies à Kikwit. *J. Infect. Dis.* 179(Suppl. 1):S87–91

[3] Bower H, Johnson S, Bangura MS, Kamara AJ, Kamara O, et al. 2016. Exposure-specific and age-specific attack rates for Ebola virus disease in Ebola-affected households, Sierra Leone. *Emerg. Infect. Dis.* 22:1403–11

[4] University of Pennsylvania School of Medicine. "Proteins found in semen increase the spread of Ebola virus infection: Penn study suggests that targeting amyloid fibrils could prevent sexual transmission." ScienceDaily. ScienceDaily, 25 June 2018. <www.sciencedaily.com/releases/2018/06/180625192629.htm>.

[5] Baseler L, Chertow DS, Johnson KM, Feldmann H, Morens DM. The pathogen-esis of Ebola virus disease. Annu Rev Pathol 2017; 12: 387-418

[6] WHO (World Health Organ.) 1978. Ebola haemorrhagic fever in Zaire, 1976. *Bull. World Health Organ.* 56:271–93

sepsis[7]. There is currently no known treatment, and thus efforts rely heavily on supportive interventions: provision of fluids (usually orally) is standard clinical practice even though its benefit is not well-documented[8]; and, if IV fluids are indicated to combat haemodynamic instability, the amount to administer in order to correct the instability is unknown and required resources may not be available[9]. It would be of interest to see interventions which have been shown to decrease mortality in resource rich settings, how these same interventions failed in resource poor nations. Some interventions which have been shown most successful in high-resource settings-- e.g. testing, IV care, dialysis, just to name a few-- were often difficult, if not impossible, to implement due to a shortage of various things including a severe shortage of well-trained staff, materials, and uniform protocols[10].

Predictors of Ebola from several studies

In a Sierra Leone cohort, results of patients (children and adults) in one ETC showed that death was "significantly associated with malaria co-infection" and that referral-time and viral load together, through their relationship to each other, were significant determinants of mortality, showing a 12% reduction of mortality with early reporting[11]. In the same cohort, predictors of death were highest with disorientation, followed by hiccups, diarrhoea, conjunctivitis, dyspnoea, and myalgia. Another cohort study in Guinea reported that the causes of death for all patients were hypovolemic shock and multiorgan failure[12]. The same study reported that hemorrhage (usually gastrointestinal) and difficulty breathing (resulting from parenteral rehydration to treat severe vomiting and diarrhea) were independently associated with death.Another study in Sierra Leone, which collected data over a 5-months period, found that the VL at admission was perhaps the most important predictor of mortality[13].

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[7] Leligdowicz, A., Fischer, W.A., Uyeki, T.M., Fletcher, T.E., Adhikari, N.K.J., Portella, G., Lamontagne, F., Clement, C., Jacob, S.T., Rubinson, L., Vanderschuren, A., Hajek, J., Murthy, S., Ferri, M., Crozier, I., Ibrahima, E., Lamah, M.-C., Schieffelin, J.S., Brett-Major, D., Bausch, D.G., Shindo, N., Chan, A.K., O'Dempsey, T., Mishra, S., Jacobs, M., Dickson, S., Lyon, G.M., Fowler, R.A., 2016. Ebola virus disease and critical illness. Critical Care 20.. doi:10.1186/s13054-016-1325-2

[8] Sprecher A, Van Herp M, Rollin PE. Clinical Management of Ebola Virus Disease Patients in Low-Resource Settings. Curr Top Microbiol Immunol. 2017;411:93-113. doi: 10.1007/82_2017_18. PMID: 28646340.

[9] Malvy, D., Mcelroy, A.K., De Clerck, H., Günther, S., Van Griensven, J., 2019. Ebola virus disease. The Lancet 393, 936–948.. doi:10.1016/s0140-6736(18)33132-5

[10] Loignon C, Nouvet E, Couturier F, Benhadj L, Adhikari NKJ, Murthy S, et al. (2018) Barriers to supportive care during the Ebola virus disease outbreak in West Africa: Results of a qualitative study. PLoS ONE 13(9): e0201091. https://doi.org/10.1371/journal.pone.0201091

[11] Hartley, M.-A., Young, A., Tran, A.-M., Okoni-Williams, H.H., Suma, M., Mancuso, B., Al-Dikhari, A., Faouzi, M., 2017. Predicting Ebola infection: A malaria-sensitive triage score for Ebola virus disease. PLOS Neglected Tropical Diseases 11, e0005356.. doi:10.1371/journal.pntd.0005356

[12] Moumié Barry, Abdoulaye Touré, Fodé Amara Traoré, Fodé-Bangaly Sako, Djibril Sylla, Dimai Ouo Kpamy, Elhadj Ibrahima Bah, M'Mah Bangoura, Marc Poncin, Sakoba Keita, Thierno Mamadou Tounkara, Mohamed Cisse, Philippe Vanhems, Clinical Predictors of Mortality in Patients With Ebola Virus Disease, *Clinical Infectious Diseases*, Volume 60, Issue 12, 15 June 2015, Pages 1821–1824, https://doi.org/10.1093/cid/civ202

[13] Gabriel Fitzpatrick, Florian Vogt, Osman B. Moi Gbabai, Tom Decroo, Marian Keane, Hilde De Clerck, Allen Grolla, Raphael Brechard, Kathryn Stinson, Michel Van Herp, The Contribution of Ebola Viral Load at Admission and Other Patient Characteristics to Mortality in a Médecins Sans Frontières Ebola Case Management Centre, Kailahun, Sierra Leone, June–October 2014, *The Journal of Infectious Diseases*, Volume 212, Issue 11, 1 December 2015, Pages 1752–1758, https://doi.org/10.1093/infdis/jiv304

Potential impacts of this proposed project

IDDO has one of the world's largest compilation of data sets of the 2014-2016 Ebola outbreak; however, from what we understand, the use of causal inference methods to analyze these individual-level data pooled across multiple cohorts has been limited, if used at all. Using IDDO's data sets, we hope to find and leverage a geographic-based instrument and implement causal inference methods to 1) better understand the determinants and predictors of mortality in EVD patients across countries, regions and/or treatment sites, and 2) provide a guidance documents to other infectious disease researchers who want to infer causality with pooled IPD. Leveraging plausibly exogenous variation in institutional and processual details of health care provision based on the backgrounds of medical officers from the affected countries of Sierra Leone, Guinea and Liberia with first-hand knowledge of the outbreak and a team with strong methodological backgrounds has the potential to yield reliable results comparable to or even better than standard regression analyses, and provide evidence-based suggestions to key stakeholders to decrease mortality in EVD patients.

Lack of methodological knowledge in our field

'Causal inference methods,' such as instrumental variables (IV), regression discontinuity (RD), difference-in-difference (DiD), fixed-effects (FE), or marginal structural models (MSM), e.g., are potentially much more effective at dealing with time-varying confounding and controlling for measured and unmeasured confounding than standard statistical methods or regression-based adjustments. Unfortunately, according to our findings in a recent systematic review, such causal inference methods are not widely implemented by infectious disease researchers who pool individual-level data, despite their utility (submission to publisher pending).

Summary of Research Objectives *(suggested maximum 200 words)*

1) Understanding if time between exposure and admission can reduce mortality in future outbreaks
2) Decreasing mortality through better understanding of determinants of EBV mortality and inverse causal relationship with supportive treatments and other factors
3) Improve on the knowledge of treatment option
4) Provide feedback about what variables to collect data on in future CRFs in order to improve future analysis efforts, to decrease mortality in the long-run

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

The primary outcome is mortality. There are no secondary outcomes as we are interested only in whether the patient survives or dies.

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

Similar to a series of quasi-experimental methods published in Clinical Epidemiology, we seek to improve infectious disease researchers' identification of opportunities to implement causal inference methods with pooled IPD across cohorts.

At this moment, based on IDDO's research agenda and the question that we have selected, we think we will be able to leverage the placement of ETCs and ETUs and create a geography-based instrument which will allow us to utilize either an instrumental variable (IV), regression discontinuity (RD), or difference-in-differences (DiD) approach in the analysis. Using one of these methods, we will be able to examine variation in treatment and intensity (e.g. OLS and IV fluid administration), and other underlying factors (e.g. viral load, malaria) and their effects on mortality.

For example, when examining the causal relationship OLS or IV fluid administration on VL and mortality, we aim to create a geography-based instrument by utilizing the distance from a patient's home to the closest and second closest ETU and, then, which ETU they actually were transported to (since this is likely as-good-as-random in such a emergency situation). By creating such an instrument, we hope to analyze those participants in a regression discontinuity, where the participants close to the threshold (x*)-- where x* is some pre-selected value of the geographical distance tool-- are like each other enough to be, nearly, indistinguishable; and thus, these participants would be as random as one would find in a randomized control trial. This, of course, hinges on the validity of the instrument (the geography-based instrument), and whether or not any "sorting" of participants can be found on either side of the threshold. If these criteria are violated, then an IV with this instrument will not be possible. If this is the case, there are several other similar opportunities available to us.

We have been informed that we should expect missing data, and, presuming that it is missing at random, we will most likely use multiple imputation. We also might want to combine this data with geography-based secondary data sources, such as facility maps created by the WHO during the outbreak, documented travel bans, burial regulations, e.g..

Full disclosure: we will not know entirely what we are able to study or measure until we access the full data set and see a) level of harmonization, b) level of curation, c) time points of variables of interest, and d) level of missingness.

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.

Is this de-identified patient data? If so, is IRB required?

We understand the gravity of the 2013-2016 pandemic, and recognize the lives that have been lost and deeply affected by this crisis. It is our hope that, should we be granted access to this data, we will be able to effectively provide helpful information to those who work on the ground in their efforts to improve survival. This is even more true now in light of the current outbreaks in Guinea and the Democratic Republic of Congo.

Sierra Leone's MOHS has been guiding and collaborating on this project from the beginning. Guidance has included but has not been limited to the provision of the questions which are most pertinent to West Africa; thus, why we have selected a potential combination of 3 of the items listed in the EDP Research Agenda (items 5, 6 , and 7). They have also provided valuable insights into the situation on the ground, as it was at that time-- which led to various unique analysis ideas. It is also my understanding that Sierra Leone's MOHS has been in touch with representatives from Guinea and Liberia who not only approved but expressed interest in close collaboration on this project. Sierra Leone's MOHS co-wrote and approved this application as we submitted it.

It is our understanding that IDDO will provide us with de-identified, anonymized data. As such, the University Hospital of Heidelberg (Universitätsklinikum Heidelberg, UKHD), does not require the permission of the ethics board at UKHD.

Dr Kwame Oneill a TDR/WHO Fellow from the Ministry of Health and Sanitation as Co-investigator has discussed this application with Dr Alie Wurie, Director of Primary Health Care MOHS, and Lawrence Babawo Senior Lecturer, Njala

University and Member Scientific Review Board MOHS Sierra Leone's. They have given their approval to the Application.

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.

We aim to publish the results of this collaboration in a top-tier journal and possibly to the Oxford University and/or Heidelberg University web page.

We also plan to disseminate this information to those severely affected by this outbreak-- Sierra Leone, Guinea and Liberia. The details of how to best disseminate this information to those most affected has not been finalized, but our discussions have ranged from 1) meetings with representatives of MOHs from Sierra Leone, Guinea, and Libera, 2) online informational sessions with both healthcare professional and community stakeholders which would use the social media platforms as a possible outlet, 3) print work and pamphlets for the community, or 4) producing and disseminating videos similar to those on COVID-19 produced b Stanford's Center for Health Education Digital MEdIC videos, https://scopeblog.stanford.edu/2020/11/09/the-power-of-animation-two-videos-offer-messages-of-hope-during-the-pandemic/.

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.

Case fatality ratios (CFRs) of EVD patients treated in West Africa during the 2013-2016 outbreak range from 70-90%[14], whereas mortality rates in EVD patients treated in resource-rich settings has been reported around 20%[15]. Because no known treatment is known, efforts rely on supportive care, particularly targeting dehydration, renal failure, and cytokine storms. However, providing supportive care to critically ill patients with EVD in resource-poor settings is challenging due to

[14] Van Kerkhove, M., Bento, A., Mills, H. *et al.* A review of epidemiological parameters from Ebola outbreaks to inform early public health decision-making. *Sci Data* **2,** 150019 (2015). https://doi.org/10.1038/sdata.2015.19

[15] Leligdowicz A, Fischer WA 2nd, Uyeki TM, Fletcher TE, Adhikari NK, Portella G, Lamontagne F, Clement C, Jacob ST, Rubinson L, Vanderschuren A, Hajek J, Murthy S, Ferri M, Crozier I, Ibrahima E, Lamah MC, Schieffelin JS, Brett-Major D, Bausch DG, Shindo N, Chan AK, O'Dempsey T, Mishra S, Jacobs M, Dickson S, Lyon GM 3rd, Fowler RA. Ebola virus disease and critical illness. Crit Care. 2016 Jul 29;20(1):217. doi: 10.1186/s13054-016-1325-2. PMID: 27468829; PMCID: PMC4965892.

limited infrastructure, lack of materials and trained healthcare personnel, and uncertainty[16].

Compounding this issue is the literature showing that interventions which may decrease mortality in resource-rich settings may actually increase mortality in resource-poor settings, e.g. administering IV fluids and nutrition is a potentially crucial treatment due to dehydration and malnutrition resulting from increase vomiting and diarrhea; however, in resource-poor settings, IV administration could cause bleeding complications, increasing likelihood of death.

In West Africa, where resources and personnel are scarce, a better understanding of the determinants and predictors of mortality may allow for resources to be more appropriately focused. This information can be distributed to health care workers, policy makers, community members, and other stakeholders.

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.

First, this collaboration between Sierra Leone's MOHS, UKHD, KUEI, and Oxford has the potential to inform key stakeholders in Sierra Leone, Guinea and Liberia, and other countries who have been affected by the virus in the future, and to better prepare those who may be affected in the future.

Second, the causal questions have been led by Sierra Leone's Ministry of Health and Sanitation, and discussed among collaborators with regards to methodological options for each question.

Third, practical knowledge of causal inference methods is a strong skill to have as a health care practitioner and policy maker. There is a hope that the product of this collaboration with the Ministry of Health and Sanitation of Sierra Leone will be shared widely through future trainings, improving the use of these methods in research efforts in the home country and region. Till Bärnighausen and Alexander Danzer are well-versed in the causal methodologies that may be used in this project.

[16] Dünser, M.W., Festic, E., Dondorp, A., Kissoon, N., Ganbat, T., Kwizera, A., Haniffa, R., Baker, T., Schultz, M.J., 2012. Recommendations for sepsis management in resource-limited settings. Intensive Care Medicine 38, 557–574.. doi:10.1007/s00134-012-2468-5

As causal inference methodology may be new to researchers in Sierra Leone, this research aims to equip Dr Kwame Oneill with the knowledge and skill of causal inference which he will then cascade to students within the College of Medicine and Allied Health science in the Department of Community Health Studies in Sierra Leone.

Fourth, should the proposed plan be successful, the publication of a guidance document on the opportunities to implement causal methods with pooled IPD from several EBV cohorts could improve and increase implementation of similar methods within the infectious disease community, potentially leading to improved health outcomes.

Funding *(suggested maximum 100 words)*

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

Kwame Oneill is funded by (WHO/TDR fellowship and Sierra Leone).

Heather Hufstedler, Lauren Maxwell and Till Bärnighausen are funded through the ReCoDID study, which is funded by the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 825746 and the Canadian Institutes of Health Research, Institute of Genetics (CIHR-IG) under Grant Agreement N.01886-000.

Alexander is unpaid for this collaboration but is funded through his professorship at the Katholische Universität Eichstätt-Ingolstadt, Germany.

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.

Olli Saarela, PhD, Associate Professor and Graduate Coordinator in the department of Public Health Sciences at the Dalla Lana School of Public Health, University of Toronto has reviewed the protocol. Her feedback has been addressed and included in the protocol as it currently stands.

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 variable list we were provided and the research agenda on IDDO's website, we would like to request the following variables:

Host factors: a) age, b) pregnancy, c) co-infections / comorbidities, d) clinical signs, e) biological signs of organ failure, f) host genetics, g) time of onset of symptoms, h) presence and duration of virus in different bodily fluids, i) health worker status /occupation, j) nutritional status, k) others.

Viral factors: a) viral sequence, b) viral exposure level, c) antibody titers / viral load evolution, d) others.

Health care factors: a) previous treatment, b) previous vaccination, time to vaccination, c) time to admission, diagnosis, and / or treatment, d) type of supportive treatment, therapeutics and/or nutrition, e) isolation, f) previous admission in holding center and timing, g) length of stay, h) others.

Disease Exposure Factors: a) History of travel to known hot spot, b) Direct contact with EVD suspected or confirmed case, c) Touching of body of An EVD suspected or confirmed case, d) Time between symptomatic onset to admission at ETC, e) Time between admission at ETC and death/discharge.

Treatment Variables: Anti-viral/anti-bacterial/rehydration therapy; Duration and dosage of treatment; Route of administration; Day of treatment start; Date of treatment completion.

Laboratory Parameters: White blood cell count; Hemoglobin; Platelet; C-reactive protein; Electrolytes; Creatinine; Liver transaminases; CPK; Lactic acid; Prothrombin; Fibrinogen (however it is worth mentioning that the coagulation factor

test was not routinely done in most ETUs although several patients may go into disseminated intravascular coagulation).

Demographics: Gender; Weight; Country of residence; Residential address (or similar); Location of Ebola treatment unit (if possible, also location of Ebola holding center); Profession.

Clinical signs and symptoms: Abdominal pain; Fever; Diarrhea; Vomiting; Bleeding; Confusion; Anemia; Body Temperature; Blood Pressure.

Disease Diagnosis: Laboratory test to Confirm Hemorrhagic fever; Date Sample Collection; Date of laboratory test.

It is important to note that the timepoints of many of these variables will determine which method(s) we can/not use. If only 2 timepoints, then our method options are limited, but more time points would expand the methodological sandbox. Similar note for non-curated, non-harmonized and missing data.