Guidance on principles and terminology for epidemiology at Epicentre

1 June 2018 v1.0

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1 Introduction

Médecins Sans Frontières (MSF) programs aim to address health problems of the most vulnerable. Responding to the direct and indirect effects of chronic and acute crises as well as to a general lack of access to basic health care in vulnerable populations through effective programs is a complex task that requires multiple competencies—all of which happen in an unpredictable environment. There is frequently a lack of reliable data on disease burden and population demographics. Even where relevant data are present, the breakdown of health systems often means there is little access to these data for relevant analyses. Drugs, vaccines, diagnostics and their programmatic delivery strategies are often woefully inadequate for vulnerable populations when transposed from rich country settings.

In such instances, epidemiology may have a role to play in helping to improve MSF programs. This may occur through describing populations and situations, providing support to program monitoring and evaluation activities, through research using observational or investigational studies. Navigating and understanding whether epidemiology can benefit the problem at hand necessitates two key understandings. First, will epidemiology help in responding to the problem or question? Second, if epidemiology is helpful, what level of evidence is appropriate? The response depends on: what is known in the literature; whether a study aims to influence international or local practice; the time available; field feasibility; and other factors.

1.1 What is epidemiology

Epidemiology[1] is the science of public health with methods relying on a systematic and unbiased approach to the collection, analysis, and interpretation of data (Coggon et al.). Epidemiologic methods depend on observation and the use of valid comparison groups to assess whether what was observed, such as the number of cases of disease in a particular area during a particular time, differs from what might be expected. Epidemiology also relies on causal reasoning based on developing and testing hypotheses to describe and explain health-related behaviors, states, diseases determinants, and events (Centers for Disease Control and Prevention, 2006).

The art of epidemiology is in knowing when, and how best, to apply the various epidemiological methods to answer specific questions. Like clinical medicine, where the best clinicians seem to sense when past knowledge applies to their patients, good epidemiologists use their own knowledge and experience to inform practice and research, using skills from medicine, biology, statistics, and public health among other disciplines.

Epidemiology has evolved conjointly, and in parallel with, Western medical knowledge. Epidemiologic thinking goes back to Hippocrates, in 400 BC (Centers for Disease Control and Prevention, 2006). John Graunt, in 1662, published the first major retrospective analysis of mortality data. His publication was the first to quantify patterns of birth, death, and disease occurrence, noting disparities between males and females, high infant mortality, urban and rural differences, and seasonal variations. In the first half of the 19th century, P.C.A. Louis paved the way for the development of rigorous investigations by using comparative data to evaluate the efficacy of bloodletting (Olsen J and C, 2007). In 1854, John Snow, recognized as the founder of what would become field epidemiology, performed the first well-documented outbreak investigation. In the mid- and late-1800s, epidemiological methods applied mainly to the investigation of disease occurrence, focusing on acute infectious diseases, whereas this was

[1] This document used both reference and source documents. The contents are derived and inspired from these examples as noted at the end of the document. Key resources are also available on the intranet as well as on wiki sites related to the conduct of epidemiology at Epicentre.

extended to noninfectious diseases in the 1930s and 1940s (Centers for Disease Control and Prevention, 2006).

Post-World War II, the discipline of epidemiology accelerated with the development of research methods and other theoretical underpinnings. The recognition of the role of chronic diseases in mortality, particularly in wealthy countries, drove much of this. In the 1980s, epidemiologic methods began to be used more formally to study injuries and violence. In the 1990s, the related fields of molecular and genetic epidemiology emerged (Centers for Disease Control and Prevention, 2006).

More recently, closely mirroring clinical medicine, in wealthy populations at least, epidemiology has also undergone technology-driven change. Large datasets, genomics, the growth of health systems research, advances in satellite images and spatial technology, increased data sharing and access, and the emergence of new disciplines—such as bioinformatics, have highlighted epidemiology's appeal as a structured approach (Centers for Disease Control and Prevention, 2006).

Epidemiology has become more expansive in scope since its first practice, with subspecialties emerging, and this expansion is not without consequences. What it means to be an epidemiologist is no longer, and perhaps never was, commonly understood. The application of epidemiologic methods to problems or situations in medicine and public health is not always obvious. Ensuring a common understanding of what epidemiology can and cannot contribute is fundamental to its practice and to the correct use of epidemiologic methods in medicine, public health, and research. In addition, not all epidemiologic evidence carries the same weight and therefore the same impact in decision-making.

1.2 Rationale

Epicentre was created in 1986 by MSF with its mission to describe the health status of populations—often displaced by armed conflict—to help prioritize activities. This also included research to evaluate existing and new tools and strategies. Answering questions on how to improve health may prevent, diagnose, and treat illness and delay death. Using the tools and principles of epidemiology to perform field epidemiology activities and conduct research relies upon an understanding of the key terminology and methods. This document aims to improve the understanding of epidemiological terms and principles at Epicentre. This is particularly important given that the distinction between field epidemiology and research is not clear-cut and is further clouded by the type of research that Epicentre conducts. Epicentre usually conducts what is sometimes called "intramural research". This type of research is conducted within MSF as an institution; this is also called "sponsor-driven research" in the context of trials of new drugs or their indications, vaccines, and diagnostics. Accordingly, there are rarely calls for proposals, and the individuals responsible for funding decisions may also be involved in the design and conduct of the research.

To help clinicians and public health professionals making the best use of epidemiological data when making decisions, study designs are categorized into "evidence hierarchies" or "evidence pyramids". The study designs providing the weakest level of evidence (expert opinions, case series) fall at the bottom , followed by case–control and cohort studies (observational studies) in the middle, then randomized controlled trials (RCTs; interventional studies); and at the very top, systematic reviews and meta-analyses of RCTs provide the strongest level of evidence. Most versions of the evidence pyramid aim to show a hierarchy of internal validity (i.e., risk of bias). Some versions incorporate external validity (i.e., applicability) or separate internal and external validity. What is important to consider within Epicentre, is ensuring that the study design is appropriate to the question or problem, accounting for a literature review of the existing evidence.

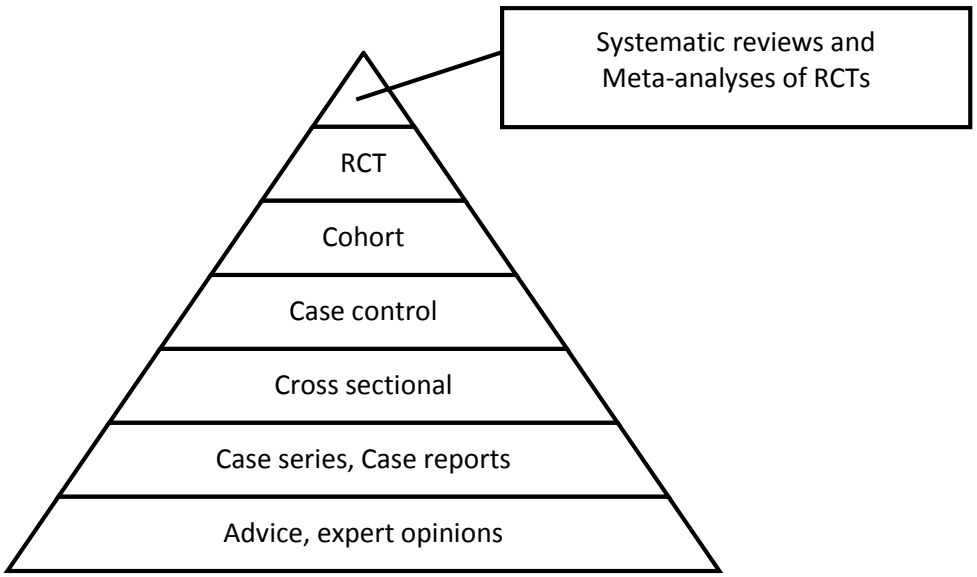

FIGURE 1: EVIDENCE PYRAMID

As such, it is important to establish general guidelines that:

- Facilitate an understanding of Epicentre's work (field epidemiology and research) among external actors and MSF by using recognized terminology;
- Ensure a common understanding of terminology within Epicentre; and
- Clarify differences between the types of studies Epicentre conducts.

2 Study design & approaches to epidemiology at Epicentre

All epidemiologic activities involve the systematic collection and analysis of data to describe disease in a population in a way that supports decision-making or knowledge. Data sources may include routinely collected program data or data collected specifically for research purposes. Epicentre conducts activities that we can classify into three broad categories: field epidemiology, observational studies (descriptive or analytic) and interventional epidemiology. In addition to these quantitative approaches, Epicentre also increasingly conducts qualitative studies. Observational and interventional studies are most often research, but this is not the case with most field epidemiology activities.

Field epidemiology includes surveillance; outbreak investigations; program monitoring and evaluations; support of health information systems (HIS); rapid assessments and providing advice and support to program teams with respect to health data collection and analysis.

Observational epidemiology relies only upon observation. Observational approaches collect information on events over which there is no control from the epidemiologist or researcher, and as such, the exposures (i.e., any factor that may either increase or decrease the risk of a disease or a health-related event) are not assigned as part of the study design. The data originate either from events observed after the start of a study or in the past. Prevalence studies, cross-sectional studies, longitudinal case series, case-control studies, cohort studies, and diagnostic evaluations are examples of observational studies.

Interventional studies, also called experimental studies, are those for which the exposure is assigned and the researcher "intervenes." These studies are characterized by the allocation of participants by the researcher to groups (or interventions). Participants are then followed to compare the outcomes of the groups. The term experimental refers to a "true experiment." This is an experiment in which one (or sometimes more) variable(s) are examined, and for which the rest are often controlled by randomization.

Two primary categories (or questions) help to understand the differences between field epidemiology, observational epidemiology, and interventional studies:

1. **Assignment of exposure:** Unlike with observational or field epidemiology, in interventional studies, the researcher assigns an exposure (for example, a new treatment, dosage, vaccine, or delivery strategy).

   Randomization: The random allocation/assignment of the exposure applies to interventional study designs. (Randomization should not be confused with "random selection" used in sampling methods.)

2. **Testing a hypothesis with a comparison group:** Researchers start with the assumption that a hypothesis (the "null hypothesis", H_0) is not true until proven otherwise, by rejecting the null hypothesis. Translation of a hypothesis into quantitative terms allows for a pre-specified degree of confidence for the rejection or acceptance of the hypothesis. All analytic studies test a hypothesis with a comparison group. Observational studies are referred as "analytic" when they involve testing hypotheses, or "descriptive" if not. All interventional studies involve hypothesis testing.

Figure 1 is a schematic overview of epidemiologic approaches. Not every type of study design or methodology is presented in this document. For example, mathematical modeling and other quantitative analyses are not discussed. This is not to negate their interest or importance. This document is not meant to be an exhaustive list; rather, it serves to provide an overview of the most common approaches to field epidemiology, observational epidemiology, and interventional studies at Epicentre. Also, other slightly different classifications of study designs might be found in epidemiological textbooks. Again, this document does not pretend to replace any textbook but to synthetize and harmonize our internal understanding and communication at Epicentre.

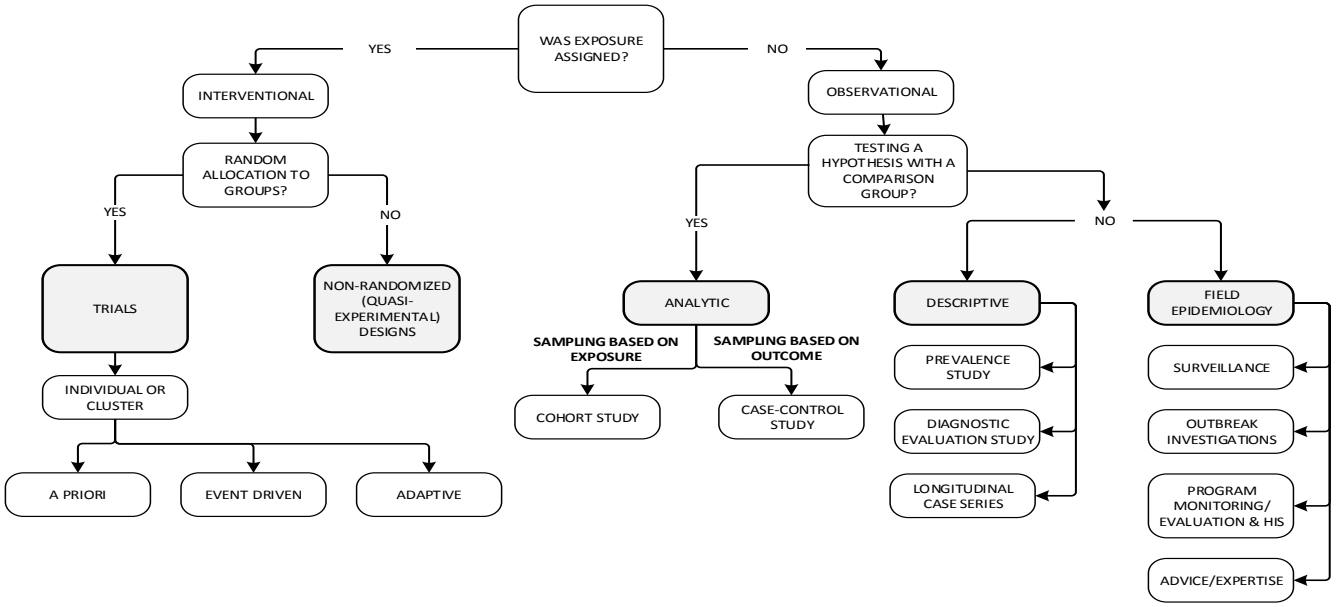

FIGURE 2: SCHEMATIC OVERVIEW OF FIELD EPIDEMIOLOGY, OBSERVATIONAL EPIDEMIOLOGY AND INTERVENTIONAL STUDIES AT EPICENTRE;

2.1 Field epidemiology

Field epidemiology serves the core function of understanding ongoing health events in a population. It provides an evidence base for programmatic goal setting and can inform research agendas for more detailed epidemiologic analyses.

2.1.1 Surveillance

Surveillance constitutes "a series of ongoing systematic activities, including collection, analysis, and interpretation of health-related data essential to planning, implementing, and evaluating public health practice closely integrated to the dissemination of data to those who need to know and linked to prevention and control" (Centers for Disease Control and Prevention, 2010). In Epicentre and MSF context, surveillance can also be thought of as "looking at what happens in the community" which is different that the routine monitoring of data from programs activities.

The aim of surveillance, which is sometimes called "information for action"(Centers for Disease Control and Prevention, 2006), is to inform program teams to allow for effective and efficient responses. This is accomplished through the systematic collection and evaluation of morbidity and mortality data and other relevant health-related information, and the dissemination of these data and their interpretation to those involved in decision-making. Given that the provision of timely information represents one of the main goals of surveillance, many systems collect a limited amount of information.

Although surveillance traditionally focuses on infectious diseases and mortality, its use extends to the tracking of injuries, chronic diseases, health clinic visits, water consumption, population movements, latrine use, telephone call volumes and other indicators. The information gathered may signal the need for further investigation.

Surveillance example:

At the end of August 2017, Rohingya families started to flee Myanmar for the neighboring region of Chittagong in Bangladesh. This led to an estimated 600,000 persons crossing the border and settling in the region. MSF-OCP organized a structured response to address the medical needs in the two areas. In order to follow the trends, a dedicated surveillance system was put in place. On a weekly basis, a sample of households selected by systematic random sampling was investigated. The data collected constituted the basis of the surveillance. Data collected included a household census, births, mortality data, the number of pregnant women, and the nutritional status (MUAC) of children between 6 and 59 months of age (MSF Operational Center Paris, 2018).

2.1.2 Outbreak investigation

Ideally, information from a surveillance system can enable the identification of a specific case or cluster of cases of a disease or syndrome. The ensuing investigation can range from a simple phone call to a full field investigation requiring the coordinated efforts of many people to characterize the extent of the outbreak and potentially determine a cause. Alerts from a surveillance system, media information, or alerts or rumors from the community can trigger such an investigation.

An investigation seeks primarily to determine the nature and magnitude of an outbreak and implement appropriate measures to address it. Data collection aims to facilitate action, rather than to ask to what additional questions the data respond. An outbreak investigation may include a research component if, for example, biological samples are stored for future or additional analyses beyond those needed to solve the immediate health problem, and/or if the data collected (available as part of the outbreak investigation itself or through additional specific data collection) allow examining risk factors (for example, through a case-control study, section 2.2.2.2)

Outbreak investigation example:

On November 4, 2010, the Ministry of Health of the Republic of Congo officially declared a poliomyelitis outbreak centered in Pointe-Noire. The declaration followed the laboratory identification of poliovirus type 1 in a patient with acute flaccid paralysis (AFP). The outbreak investigation implied the individual data collection for each patient fitting the AFP case definition. These data allowed describing the outbreak in terms of time, place and persons.

In addition, a survey was conducted in the community to investigate conditions potentially contributing to the outbreak, including vaccination coverage. Low vaccination coverage and no previous exposure to wild poliovirus likely led to an accumulation of susceptible persons (Le Menach et al., 2011).

2.1.3 Program monitoring and evaluation

Program monitoring and evaluation (M&E)[2] includes a variety of methods that, at their core, are cycles of planning, action, and reflection. M&E activities can also take place outside of epidemiology, and usually do, for example, in finance or human resources.

Monitoring is the ongoing systematic collection and analysis of information about a program undertaken to assess progress toward the achievement of objectives, outcomes, and impacts. Results are sometimes incorporated into alert systems. Questions generated from monitoring activities ask whether a program is on time, on target, and on budget. Monitoring activities typically feed into evaluation activities.

Monitoring activities often focus on parts of a program, but can also encompass an entire set of program data. For example, determining the frequency of missed opportunities for vaccination among patients or participants monitors one aspect of that program.

Evaluation is a broad term that refers to the systematic use of scientific methods to examine the implementation, utility, and other characteristics of a program or its components (Centers for Disease Control and Prevention, 2010). Evaluation seeks to assess the historic and current necessity of a program. It considers the ways—including the appropriateness of such ways—by which programs address problems and recommends improvements. It involves the periodic, retrospective assessment of a program, conducted internally or by external evaluators.

For MSF, evaluations normally consist of assessments of the design or strategy, implementation, and results of interventions against established MSF or international standards, humanitarian principles, MSF policy, and country strategy (Kampmuller, 2017).

[2] M&E is sometimes referred wrongly as Action Research. Action Research is an approach rather than a method itself and includes a participatory element.

Program evaluations, a subset of evaluations, refer to the systematic application of scientific and statistical procedures for assessing the conceptualization, design, implementation, and utility of a program; use of the resulting information seeks to optimize program outcomes (Coughlin, 2006). Operational research[3], implementation research, and health systems research all contribute to overall program evaluation. Epicentre does not regularly perform implementation or health systems research.

Program monitoring and evaluation example:

The FUCHIA software (Follow-up and care of HIV infection and AIDS) facilitates both the clinical and biological follow up of HIV-infected patents and the evaluation of HIV/AIDS programs in developing countries. This software encompasses data collection and the production of automatic reports. Reports generated are directly linked with output indicators allowing for the assessment of program activities compared with targets (Poulet, 2015).

2.1.4 Advice and support

Providing technical advice and support constitutes another component of field epidemiology. In certain situations, field teams or other staff members may require the advice or temporary support of an epidemiologist. This may entail a conversation or discussion concerning a situation in the field or a specific medical problem. This may not require anything more than a phone call, but may also involve a structured and deep review of data or other documents. Many mathematical modeling activities fall here, where the aim is to generate hypotheses, make projections, and clarify options for decision-making.

2.2 Observational epidemiology

2.2.1 Descriptive

Descriptive epidemiology refers to the characterization of the distribution and/or trends (which can sometimes involve only one case or death) in health and disease over time, place and groups of persons. It provides information for planning health programs and prioritizing activities.

2.2.1.1 Prevalence studies

Prevalence studies are cross-sectional observational study in which a sample of persons from a population is enrolled and their exposures and health outcomes are measured simultaneously. The cross-sectional study measures the presence (prevalence) of a health outcome at a point in time irrespective of duration. For example, in a cross-sectional study of HIV-positive persons, some enrollees may have lived with HIV for many years, while others may have only recently been infected.

[3] "From a health program perspective, operational research may be defined as: *The search for knowledge on interventions, strategies or tools that can enhance the quality, effectiveness or coverage of programs in which the research is being conducted" ZACHARIAH, R. & KARRIES, K. 2010. Operational Research: Definition, purpose & procedures (A policy framework). Brussels Operational Center: MSF - Brussels, Medical department (Operational research)..*

When data about a disease are collected together with data on its potential determinants in a cross-sectional study, epidemiologists may develop hypotheses and test them by comparing several groups. However, "from an analytic viewpoint, the cross-sectional study is weaker than either a cohort or a case-control study (described hereafter). This is because a cross-sectional study usually cannot disentangle risk factors for the occurrence of a disease (incidence) from risk factors for survival with the disease" (Centers for Disease Control and Prevention, 2010). Cross-sectional studies are used routinely to document the prevalence of health states in a community (e.g., the prevalence of vaccination against measles) and outcomes (Centers for Disease Control and Prevention, 2010).

It is important here to note that coverage surveys (i.e., vaccination or nutritional program coverage surveys) follow a cross-sectional (observational) design although are evaluation activities.

Prevalence study example:

The Aka Pygmy communities living in northern Congo have almost no access to healthcare and, as a result, are still affected by the neglected disease known as yaws. A community based prevalence study was conducted to estimate yaws prevalence and found the serological prevalence was 13.0% (95%CI: 9.9-17.0). This study was a part of the first implementation of the WHO recommended universal treatment strategy with a single oral dose of the antibiotic azithromycin (Coldiron, 2012).

2.2.1.2 Diagnostic test evaluations

A diagnostic test entails any kind of medical test performed to aid in the diagnosis of a suspected disease or condition. Such tests may be used as a component of diagnostic algorithms and/or as screening tests. Assessed according to validity, sensitivity, specificity and other criteria, the evaluation of diagnostic tests occurs for individual tests (e.g., rapid diagnostic tests) as well as for algorithms employing multiple diagnostic tests. These studies are principally descriptive.

Diagnostic test evaluations example:

Results of three rapid diagnostic tests (RDTs) for the diagnostic of malaria were compared to blood smear microscopy (the gold standard method) in children <5 years of age living in high vs. low malaria intensity settings in southwestern Uganda. The results of the study found long time for one type of RDT to become negative, considerably reducing its specificity. The choice of the RDT for low vs high transmission settings should balance the risks and benefits of over-treatment to the risks of missing malaria cases (Grandesso et al., 2016).

2.2.1.3 Longitudinal case series

Longitudinal case series follow study participants with a disease or health condition over time, with continuous or repeated monitoring of risk factors, health outcomes, or both. This type of study represents descriptive epidemiology and seeks to formulate hypotheses. Longitudinal case series should not be confused with the cohort study—which is a specific type of analytic study described below, nor with a

surveillance system—which usually does not follow individuals. Longitudinal case series collect a variety of information on participants, who are simply followed, but not compared with, a control group. Conclusions are made with respect to a disease process for a specified amount of time (i.e., over the course of a hospitalization, throughout an acute illness, during a treatment, or other disease characteristics for a fixed period—such as one year). Data can be collected retrospectively or prospectively and may include biological samples. It can be difficult to distinguish between a longitudinal case series and program monitoring activities. Longitudinal case series aim to respond to specific questions concerning individual patients, rather than programs.

Longitudinal case series example:

HIV-positive inpatients aged ≥13 years were studied from two programs in Kenya and the Democratic Republic of Congo (DRC). Clinical and demographic characteristics and hospitalization outcomes were assessed. Data were collected prospectively at the Kenya site, and retrospectively at the DRC site, for those admitted with HIV-1 disease from January to March 2015 (Kenya) and May to July 2017 (DRC) (Ousley et al., 2018).

2.2.2 Analytic studies

Analytic studies assess whether defined groups with different frequencies of disease differ in their demographic, immunologic, behavioral, or environmental exposure, or any other so-called potential risk factors. Ideally, the findings provide sufficient evidence to direct effective responses. Analytic epidemiology can extend beyond the simple identification of risk factors to determine causal pathways and evaluate the effect of specific interventions (e.g., diagnostics, treatment, vaccines) or packages of interventions.

The key feature of analytic studies is the presence of a comparison group allowing for hypothesis testing; descriptive studies do not include a comparison group.

2.2.2.1 Cohort study

Cohort studies are based on identifying participants as exposed or unexposed, and looking at outcomes, either based on data collected retrospectively or prospectively.

In a cohort study, the epidemiologist records whether each study participant is exposed or not, and then follows the participants to see if they develop the disease of interest. This differs from an experimental study because, in a cohort study, the investigator observes rather than determines the participants' exposure status. After a period of time, the investigator compares the disease rate in the exposed group with the disease rate in the unexposed group. The unexposed group serves as the comparison group, providing an estimate of the expected amount of disease occurrence in the absence of exposure. Since the definition of the study group is by exposure, cohort studies can thus look at multiple health outcomes.

There are many important differences between a cohort study and a longitudinal study / case series (section 2.2.1.3 above). The most important is the presence of a comparison group.

The following is an example of a follow-up or **prospective cohort study**, characterized by the enrollment, at the study start, and prospective follow-up, over time, of participants to identify the occurrence of the outcomes of interest.

Prospective cohort study example:

A prospective cohort study was conducted in Niger to compare the incidence of wasting, stunting, and mortality among children aged 6 to 36 months who were receiving preventive supplementation with either ready-to-use supplementary foods (RUSFs) or ready-to-use therapeutic foods (RUTFs) as part of the MSF program. Children in this study were given a monthly distribution of RUSFs or RUTFs during a period of 6 or 4 months and their outcomes were compared (Isanaka et al., 2010).

An alternative type of cohort study is a **retrospective cohort study**. In this type of study both the exposure and the outcomes have already occurred and data are collected retrospectively. Just as in a prospective cohort study, the investigator calculates and compares rates of disease in the exposed and unexposed groups.

Retrospective cohort study example:

A retrospective cohort study was conducted in Kenya to assess the effect of single-dose doxycycline in the prevention of cholera. Watery diarrhea episodes and intake of doxycycline were assessed retrospectively amongst family members of confirmed cholera cases comparing those that took doxycycline to those that did not. (Lecossais and Grandesso, 2016).

It is important to consider that retrospective cohort studies can often be conducted more quickly, but are a weaker approach than prospective cohorts as the exposure is usually more difficult to estimate.

2.2.2.2 Case control study

Case-control studies select participants based on their disease status and assess previous exposures. Investigators start by enrolling a group of people with a defined disease or condition. As a comparison group, the investigator then enrolls a group of people without disease (controls), representing the population from which the cases originated. Investigators next compare previous exposures between the two groups. The control group provides an estimate of the baseline or expected amount of exposure in that population. If the amount of exposure among the case group is substantially higher than the amount you would expect based on the control group, then the illness is said to be positively associated with that exposure and inversely, protected by that exposure when higher in the control group. Similar to a cohort study, the “cases” in a case-control study can be enrolled prospectively or retrospectively. Prospective data collection is usually preferred because they limit a variety of biases, but sometimes, particularly in outbreaks, only retrospective data collection may be possible.

Case control study:

A case-control study in Magaria, Niger looked at the protective efficacy of seasonal malaria chemoprevention against developing clinical malaria. Children aged 3 to 59 months diagnosed with malaria were matched by age, village, and date of distribution to three community controls with no malaria. The quantification of the intake of the chemoprevention among the cases and controls was assessed to estimate its protective efficacy against clinical malaria (Coldiron, 2017).

2.3 Interventional

2.3.1 Trials

Experimental/interventional studies are often called trials. For our purposes, a **trial** is defined as a research study in which one or more participants are prospectively assigned to one or more interventions (which include a control (best available intervention or placebo) to evaluate the effects of those interventions on health-related outcomes. The investigator determines, through a controlled process, the exposure for each individual or community and then tracks the individuals or communities over time to detect the effects of the exposure. Trials include strict criteria for the inclusion and exclusion of participants, the allocation of treatment a priori (i.e., by randomization; and thus RCT), and the enforcement of a particular protocol.

Trials can be distinguished as follows (Rothman et al., 2008):

- **Clinical trials:** In which participants are patients admitted to care in a health structure and the intervention aims to cure or prevent death or disability;
- **Field trials:** In which participants are not patients.

Trials can be designed to randomize participants individually or by group (cluster randomized trials). Trials can be implemented in one or multiple sites, can be analytical or pragmatic. There are numerous trials designs (e.g. parallel, cross-over, etc), different trial objectives (e.g. non inferiority trials, equivalence trial) and phases in the development of a new product (e.g. phase I, II, III, IV). Randomization can also take many forms, depending on the type of study design, objectives, setting and feasibility considerations among others. There are three major types of randomization. These randomization approaches may be directed at the sample size and allocation (**adaptive**); may be based on **a priori** assumptions to generate hypotheses of sample sizes and other statistical attributes; and may also be **event-driven**. The type of randomization and approach to trial design is a vast area of research and discussion. All have their own methodological specificities but these considerations fall beyond the scope of this document.

Well-conducted trials are based both on the principles of experimental design and on respect for the rights of study participants. Efficient designs (i.e., those that produce the intended results with minimum resource expenditure—money, participants, time, etc.), that also lead to unbiased conclusions, are critical.

Clinical trial example:

In view of the costs and consequences of the emerging resistance associated with routine antibiotic use, this clinical trial investigated the routine use of antibiotics at admission to a nutritional treatment program. In a double-blind, placebo-controlled trial in Niger, researchers randomly assigned children 6 to 59 months of age with uncomplicated severe acute malnutrition to receive amoxicillin or placebo for seven days. The primary outcome was nutritional recovery at, or before, week eight. The study found no benefit to routine antibiotic use with respect to nutritional recovery from uncomplicated severe acute malnutrition in Niger (Isanaka et al., 2016).

It is important to note that the use of the term "pragmatic trial" is often a misnomer. The Consolidated Standards of Reporting Trials (CONSORT statement) focuses on explanatory trials (investigating an intervention in ideal circumstances) but now contains an extension for pragmatic trials (investigating an intervention in everyday practice). Pragmatism is a quality or attribute of the trial that is not a dichotomy. Most trials will have some aspects that are explanatory, and some that are pragmatic, and use of the pragmatic extension is meant to clarify aspects of the trial. Use of the term pragmatic in describing a trial should be done with caution and not used as an excuse to relax scientific or ethical standards. The degree of pragmatism of an RCT can be evaluated by trial investigators using the PRECIS-2 tool, a tool that comprises 9 domains, each scored from 1 (very explanatory) to 5 (very pragmatic). Understanding the extent to which a RCT is pragmatic will help understand how relevant it is to real-world practice (Dal-Ré et al., 2018).

2.3.2 Non-randomized or quasi-experimental designs

A quasi-experimental design lacks random assignment to an intervention or control group. Use of this type of study occurs when it is not possible to randomize. A quasi-experimental design identifies a comparison group that is as similar as possible to the intervention or treatment group in terms of the baseline characteristics. While potentially more practical than a trial, this study design often introduces bias when the experimental and control groups are not equivalent. These types of studies are also sometimes referred to as "natural experiments."

Natural experiment design example:

A stock-out of first line standard antimalarial drugs at an Ebola treatment center in Foya, Lofa County, Liberia, for a 12-day period in August 2014 triggered a natural experiment. During this time, patients received the combination drug artesunate–amodiaquine; amodiaquine is a compound with anti–Ebola virus activity in vitro. No other obvious change in the care of patients occurred during this period. Investigators fit unadjusted and adjusted regression models to standardized patient-level data to estimate the risk ratio for death among patients with confirmed EVD who were prescribed artesunate–amodiaquine (artesunate–amodiaquine group), compared to those who were prescribed artemether–lumefantrine (artemether–lumefantrine group) and those who were not prescribed any antimalarial drug (no-antimalarial group) (Gignoux et al., 2016).

2.4 Qualitative methods

Qualitative research is characterized by its aims, which relate to understanding some aspect of social life, and its methods, which in general generate words rather than numbers (Brikci and Green, 2007). In addition to the "what, where, when" questions of epidemiology, qualitative methods also help to answer the "how" and "why" questions that are not always amenable to quantitative measurement, such as those concerning beliefs and behaviors (Pope and Mays, 1995). Qualitative methods are often employed in conjunction with other studies, particularly for experimental/interventional studies.

The goal of qualitative methods is to understand social phenomena in natural rather than experimental environments. Data are generated by different types of interviews with individuals (e.g., general or key informant) and group discussions (e.g., natural group interviews, focus groups). In addition, contextual data can be collected through the use of observation, analysis of reports, and through oral data such as informal conversations and stories (Brikci and Green, 2007).

There are several approaches to analyzing qualitative data, but thematic analysis is sufficient for most applied projects. This requires reading and annotating transcripts to identify themes. Coding themes are developed and then applied to the data, after which similarly coded data are extracted and grouped for the identification of patterns and relationships. In addition, a narrative analysis is required to tell the story of the issue being investigated (Brikci and Green, 2007).

Validity of findings are increased using a process called triangulation where evidence is sought using a wide range of sources and the results are compared for convergence.

It is important to recognize that it is generally difficult to extrapolate or generalize findings from qualitative research.

2.5 Ethical considerations

The following section is not an exhaustive list of ethical considerations, but a starting point.

Any study, epidemiological activity or research activity involving human participants or the use of human biological samples must be done ethically. It must adhere to accepted norms and practices in research ethics, such as those set out in the CIOMS International Ethical Guidelines (Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization, 2016) and the World Medical Association Declaration of Helsinki – Ethical Principles for the Medical Research involving Human Subjects (World Medical Association, 2008). Scientific and methodological soundness is an essential pre-requisite for ethics soundness. Research must aim to be scientifically valid, accurate, and appropriate.

The principles of biomedical ethics devised by Beauchamp and Childress (Beauchamp and Childress, 2012) provide a framework from which to approach common ethical issues. These principles are:

- Autonomy: The right for an individual to make his or her own choice;
- Beneficence: The principle of acting with the best interest of the other in mind;
- Non-Maleficence: The principle that "above all, do no harm" as stated in the Hippocratic Oath;
- Justice: A concept that emphasizes fairness and equality among individuals.

Ethical issues of concern include, but are not limited to:

- **Minimizing risks and enhancing benefits:** Risks posed by experimental trials are often greater than other types of studies. However, any type of research may result in burden: a loss of privacy, time spent completing interviews and examinations, and possible adverse psychological effects—such as enhanced grief or false expectations. There are also risks associated with therapeutic misconception, and in particular for MSF-settings, philanthropic misconception. These risks are of particular concern in vulnerable populations. Benefits are often societal in nature, such as obtaining new information about the causes of disease or identifying health disparities across groups defined by ethnicity or other factors.
- **Obligations to communities:** This is a key consideration for MSF, which evokes the principle of justice broadly. It represents a range of possibilities, from participatory action research, to collaborative partnerships, to benefit-sharing and post-trial access. In addition, research obliges the communication results of studies at the earliest possible time after appropriate scientific review so that the widest possible audience stands to benefit from the information.
- **Free and informed consent:** The obtainment of informed consent (most often but not exclusively written) ensures that participants have voluntarily chosen to participate, free from coercion and/or undue inducement. Free and informed consent gives the legal authorization to proceed with research. This necessitates the provision of information on which to base decisions regarding participation in the research and includes the purpose, risks, benefits, and right to refuse. Exceptionally, informed consent may be waived by an ethical review committee, taking into account at minimum, minimal risk, social value and real unpracticality to obtain consent amongst other factors. Issues with informed consent for vulnerable populations include the misinterpretation of study participation as health provision; in addition, study participants may not feel they can opt out if a person of authority is requesting consent.
- **Privacy and confidentiality:** Regulations to protect the privacy of participants and confidentiality of health records must be adhered to and followed. Notably, the protection of any individual-level

study data, including their secure retention[4], transmission[5], or transfer[6] is essential for patient privacy. In short, the system hosting such data should be secured to prevent unauthorized access and the movement of any individual-level data must be encrypted.

All of the above apply to field, observational, and interventional epidemiology. In addition, it is important to note areas that may often be overlooked.

First, there are ethical considerations in the practice of programs and routine medical care, where participants must demonstrate the voluntary nature of their participation. Vaccination campaigns are an example. There are in fact separate bodies of knowledge and guidance on medical and public health ethics.

Second, surveillance and program monitoring activities involve the regular, ongoing collection of health-related data. Registries require governance structures, approval processes, and ethics oversight to aim for a favorable risk-benefit ratio. Risk (i.e. the probability of harm) needs to be minimized, while anticipated harms need to be minimized or mitigated. The benefits of collecting the data must be balanced with the possible risks and harms to participants, such as the risk of confidentiality breach and harm associated with disclosing a person's disease status or membership in a group. Data should be anonymized and should not be collected if they will not be used. Steps taken to maximize potential benefits include ensuring the quality of data collected (i.e., accurate, complete, and timely). Risks are associated with breaches of confidentiality, which are of particular concern with technological advances to disseminate data over several external memory devices and over the internet.

There are many resources available on ethical issues in field epidemiology and research and it is important to incorporate debates and developments at all stages of the activity.

2.5.1 Ethical review

All MSF research is always subject to ethics review in the study countries and by MSF ERB. For some categories of research (surely for clinical trials) most countries also require the approval of the national regulatory authority.

The purpose of ethical review is to ensure that studies or activities are designed to conform with relevant ethical standards and the rights and welfare of participants are protected. The use of ethics review boards (ERBs) in research is well accepted; however, the use of ERBs for field epidemiology activities is not always clear and sometimes ignored. Institutional Review Boards (IRBs) are also used; they serve as a joint ethical and institutional review.

It is important to highlight that the classification of activities into the categories of "epidemiology in practice" or "research" does not absolve anyone of ethical obligations imposed by ERBs, including the MSF ERB. While the ethical requirement of review by an ERB is not universally defined for research and practice activities, considerations of consent and confidentiality apply equally to both activities. Where practice and research intersect, careful consideration should be made with respect to any ethical issue that would benefit from third party review (Coughlin, 2006).

When there is confusion as to whether ERB review is required, it is important to obtain guidance from the MSF ERB as well as those of the national authorities.

[4] Retention refers to the storage of data on physical devices such as computers, flash drives, and CDs.
[5] Transmission refers to the movement of data over the internet from the study sites.
[6] Transfer refers to movement of data to other entities.

The MSF Research Ethics Framework is meant to encourage researchers to think critically about their protocols, justify their methods, think about possible harms and benefits, and consider what the implications of their research might be. It also includes considerations particularly relevant to MSF's research, such as use of biological material and dissemination of research findings. Finally, it describes the conditions under which research may be exempted from ERB review, by knowing that these protocols may still be subject to ethics review in the study country (Medecins Sans Frontieres, 2013). These conditions for exemption include:

- A posteriori analyses of routinely collected clinical data (that fulfill the criteria as set out by the MSF ERB).
- Standardized surveys (i.e., mainly nutrition surveys, immunization surveys, mortality surveys) where the standard protocol has been pre-approved by the ERB, if no more than minimal changes have been made to the protocol (and these changes are underlined and justified) and if certain criteria have been met.
- Sensitive surveys (e.g., mental health, sexual violence) always have to undergo ERB review.
- Routine program implementation and assessment related work which may include surveillance activities; and,
- Monitoring and evaluation as part of the normal implementation of projects.

The Medical Director of the Operational Center involved in the research is responsible for making exemption decisions, after review of study-related information (e.g. most often a comprehensive protocol). For projects outside of MSF, the Epicentre Director responsible for the project determines exemption decisions.

3 Documentation for field epidemiology

Field epidemiology activities must support the need to provide pertinent and robust information quickly to facilitate decision-making. When these activities are slow, this can have a negative impact on patients, participants, populations, and programs. Overly complicated field epidemiology activities can introduce delays and unnecessary confusion as well as unrealistic expectations. Slowing down the implementation of monitoring and surveillance activities can prevent MSF program staff from having the information they need to improve and orient operational and medical decision-making. However, this aspect of field epidemiology does not preclude the importance of appropriate documentation.

Every field epidemiology activity should include a Terms of Reference (TOR) document that explains the objectives of the activity, timeline, resources overview and expected results. The TOR should also include information on the communication and dissemination of results.

Surveillance and outbreak investigations constitutes activities requiring rapid reactivity; they should be put in place as quickly as possible and defined with the MSF Operational Center (OC) or external partner

requesting the work. Additional documentation may be needed, in particular Material Transfer Agreements if samples are to be collected, analyzed, and possibly shipped.

Many program-monitoring activities require a summary document on what analyses will be performed so that ERB exemption can be determined as discussed previously (section 2.5.1). This document should include the rationale for the activity, data sharing plan (if relevant) and partnerships, analysis plans, ethical considerations, and dissemination of results. Occasionally, a full protocol (section 4.1) may be required, in which case it is important to consider the consequences on the activity itself in terms of delay (i.e., delay associated with the time required to draft a full protocol and apply for ethical review or exemption of the activity). The potential benefits of the activity need to be carefully weighed against any delays that may be induced.

It is also important to note that, if protocols for vaccination coverage as well as for retrospective mortality surveys have been pre-approved by the MSF-ERB, this may not preclude the need for national ERBs in some cases, but provide a useful resource to ensure timely implementation. In some instance, national ERBs/Ministry of Health might also request the use of their own standard protocols.

KEY ROLES AND RESPONSIBILITIES OF A LEAD FIELD EPIDEMIOLOGIST

Investigates outbreaks and other health emergencies; uses routinely-collected data to form hypotheses that may require further investigation. Advises on methodologies for surveillance and program monitoring, including the development of indicators. Coordination and planning; synthesizing information from diverse data sources; data cleaning and analyses; communications and report writing. The Lead Epidemiologist must be physically present in the field. There may be some exceptions to this depending on the activity (ex, expertise).

4 Practical guidance for observational studies

Observational studies frequently use data routinely collected by MSF programs, to provide ways of improving operations, and deliver more effective, efficient, and equitable care. More often than not, observational studies conducted in Epicentre can be considered as operational research. Operational Research is predominantly of use to health care providers. It tends to address a local problem, taking into account the particular context in which it occurs, with the goal of enhancing the quality, effectiveness, or coverage of the specific program being studied (Remme et al., 2010).

4.1 Documentation requirements

Every observational study should have a written protocol that states the goals of the study, provides a background and rationale for the study, specifies the criteria for inclusion and exclusion, outlines the methods and timing of follow-up, gives a precise definition of the anticipated outcome measures, and gives the details of the study design, an overview of the study procedures and of its ethical considerations

(including information notice and consent forms). The study design should minimize the possibility for bias in the interpretation of the results. Any substantial changes to the conduct of the study, including modifications of the sample size, eligibility criteria, or treatment regimens, should be reflected in amendments made to the protocol and approved by co-investigators and relevant ERBs.

The protocol is a narrative document, providing information about the study and serving as a study reference (i.e., a study manual or overview). Study protocols, although they contain standardized information, are all different. General guidelines and templates are available for different types of protocols, but it is important to remember that a protocol is specific to the research question or hypothesis, location(s), context(s), study team, population, and design. As such, although there is much to be learned from reading and writing protocols, each study has its own unique protocol. Furthermore, protocols are living documents, meaning that they should reflect the study at present and serve as a guide. Revisions and unforeseen event necessitate protocol amendments, with different versions of protocols tracked and maintained for record-keeping. Naming and numbering conventions should follow Epicentre's SOP for naming and version control.

It is not uncommon to develop a study where the site(s) of the study is(are) not yet known. This is often the case for emerging or epidemic-prone infectious diseases. A master protocol sets out an overview of the study and then site-specific protocols may be put in place in advance of the study and submitted to the MSF ERB a priori. Both the master protocol and site specific protocols should be developed in advance. It is important to note that the term "generic" protocol should be avoided and instead the term "master protocol" be used. The first page of the protocol should include:

- Study title
- Coordinating institution (this is usually an MSF OC that is financing and participating)
- Principal Investigator (PI)
- Co-investigators
- Study site(s)
- Study type
- Partners

Consultation of technical advisors (or of a steering committee) calls for a document defining the roles, responsibilities, and expectations of the technical advisors. This "roles and responsibilities document" should be included in an appendix of the protocol. This is different than a scientific committee (discussed in section 5). Steering committees contain a mix of technical advisors as well as operational persons and may represent different institutions.

Epicentre protocol templates (for uniform formatting) are available for observational studies and all protocols should use standardized reporting guidelines. These guidelines are a minimum set of recommendations for reporting different study designs. They offer a standard way to prepare reports of study findings, facilitate their complete and transparent reporting, and aid readers in their critical appraisal and interpretation. Standardized reporting guidelines are available for most study designs and it is the responsibility of the Principal Investigator (PI) to ensure compliance. Documentation of these guidelines should be noted in the protocol. For example, for observational studies there is the Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (The Equator Network: Enhancing the quality and transparency of health research, 2010).

Documentation in addition to the protocol may be needed in particular: Material Transfer Agreements if samples are to be collected, analyzed, and possibly shipped and Memorandum of Understanding or Research Collaborative Agreement if external partners are involved.

4.2 Data management and analyses

Protocols should include a data sharing plan (if relevant) and management plan. If statistical analyses will be performed, a statistical analyses plan should be described fully within the protocol. Sufficient detail should be provided so that data collection, quality assurance, analysis, and archiving of data and all study documents[7] are clear. Enough information needs to be provided so that a reader can understand and replicate the study.

The use, storage and possible destruction of biological materials should also be clearly stated in the protocol.

4.3 Organization and oversight

Observational studies require a defined set of skills and competencies. These skills may be related to basic scientific and/or medical knowledge, statistics, field experience, knowledge of the program, scientific writing, and experience with similar studies, to name a few.

Just as the methodology section of a protocol details how a study will be conducted, the study organization and oversight section provides information on the specific individuals responsible for each task. Each individual named in the protocol should have a clear role and associated responsibilities, which can be easily identified in the text of the protocol.

Table 1 provides an overview of the different roles within an observational study.

TABLE 1: KEY ROLES AND RESPONSIBILITIES IN OBSERVATIONAL STUDIES AT EPICENTRE

KEY ROLES AND RESPONSABILITES	DESCRIPTION
Study Supervisor	Assumes responsibility for the overall integrity of the study. This position arises when the Principle Investigator requires technical oversight. The Study Supervisor assumes responsibility for ensuring the conduct of the study through completion. Usually the Departmental Director fulfills this role, but in some instances, this may be an epidemiologist at Epicentre. This is determined on a case-by-case basis. This role is a specific role in the study, and if not present in a study, does not negate the managerial role of the Departmental Director.
Principle Investigator	Assumes overall responsibility for the conduct of the study which includes, but is not limited to, protocol writing, development of data management and analyses plans, ethical aspects and coordination between the MSF program and study staff (if applicable). The PI of the study must be present in the field(s) (i.e., at the study site(s)).

[7] Medical/case report forms, laboratory forms, questionnaires, consent forms etc.

Co-Investigators	Devotes a specified and quantifiable percentage of time to the study. Co-investigators may also be responsible for specific scientific aspects of the study (e.g., data management and statistics, laboratory analyses, medical care).

It is important to note that Epicentre does not allow for "honorary" investigators. It is important to recognize there that some investigators may be requested by the ERB or Ministry of Health. This should be discussed on a case-by-case basis with the Study Supervisor. Principle Investigators must be present in the field(s) (i.e., at the study site(s)). Individuals who are included as co-investigators must have an established and identifiable role in the study and devote a traceable percentage of their time. Facilitating or coordinating discussion about the study, nor an institutional affiliation alone, is not sufficient to be a named co-investigator. Individuals providing advice to the study, or facilitating approvals or discussion, can be named as other contributors, but not as co-investigators, as long as this advice is substantial. For additional information, please refer to the forthcoming section on misconduct (Section 6).

A study organizational chart (organigram) should be included in every protocol. Figure 3 is an example of how an observational study might be organized and the structure of the oversight therein. The Departmental Director determines any need for oversight, based on the competencies and skills of individuals.

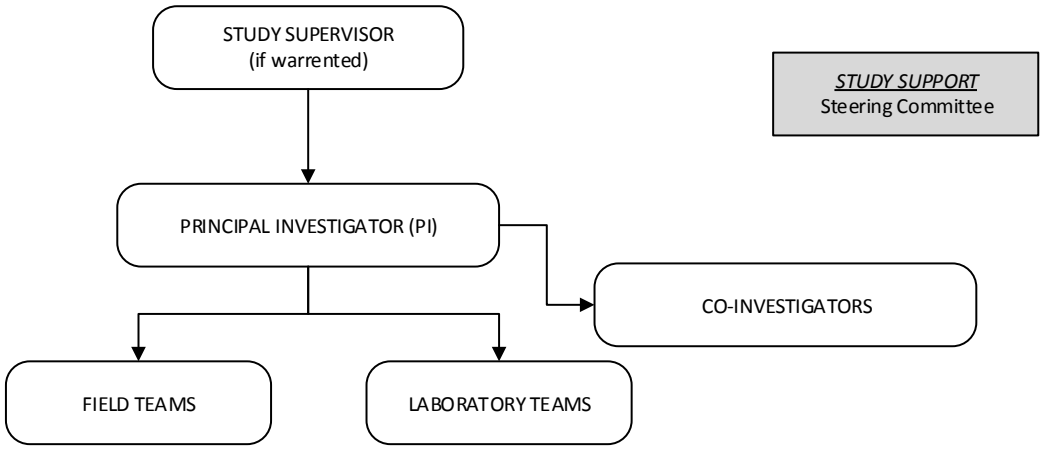

FIGURE 3: SAMPLE ORGANIGRAM OF THE CONDUCT OF AN OBSERVATIONAL STUDY

5 Practical guidance for interventional studies

5.1 Documentation requirements

5.1.1 Protocol

Similar to observational studies, every interventional study should have a written protocol that states: the goals of the study and the hypothesis/hypotheses to be tested and necessary sample size, provides a background and rationale for the study, specifies the criteria for inclusion and exclusion, outlines the methods and timing of follow-up, gives a precise definition of the anticipated outcome measures and potential adverse events, and gives the details of the study design, an overview of the study procedures and ethical considerations (including information notice and consent forms). The study design should minimize the possibility for bias in the interpretation of the results. Any substantial changes to the conduct of the study, including modifications of the sample size, eligibility criteria, or treatment regimens, should be reflected in amendments made to the protocol and approved by co-investigators and relevant ERBs.

Certain information about the proposed study should appear on the cover page of the protocol. For trials of new vaccines, and therapeutics, Epicentre follows the WHO template. It is important to note below that different terminology may apply for studies for which Epicentre is the Sponsor or has been delegated the responsibilities of the Sponsor by MSF. For all studies, the following information should be included:

- Study title
- Registry and protocol number (see Epicentre guidance document on when registry is required)
- Coordinating institution (or Sponsor for investigational products)
- Study Director
- Principle Investigator (or Sponsor's PI—for investigational products—or Coordinating PI)
- Co-investigators and Site Co-investigators if applicable
- Site PI if applicable
- Monitoring (internal and external)
- Study site(s)
- Study type
- Name of study statistician(s)
- Partners

Each study should have clearly articulated research objectives, achievable from successful execution of the study design. This includes a clear statement of the primary objective. A summary of the study design should be included in the protocol. Every effort should be made to ensure standardized reporting guidelines can be adhered to when planning and executing the study. The CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline is intended to improve the reporting of parallel-group RCTs, enabling readers to understand a trial's design, conduct, analysis, and interpretation, and to assess the validity of its results (The CONSORT Statement). Guidance for other study designs is also available.

The Principal Investigator, at least, will sign the final version and subsequent amendment(s) of the protocol. A summary of protocol changes are kept for each new protocol version by saving the tracked-changes version with the new version/amendment. These versions are saved and archived following Standard Operating Procedures (SOPs). There are specific SOPs for research at Epicentre and all SOPs should be followed; they are not described fully here.

5.1.2 Scientific Committee

The composition of the **Scientific Committee** should include recognized external experts in the field of study. Terms of reference for the scientific committee should be developed and agreed upon for the benefit of the members as well as the study team. The Study Director convenes the Scientific Committee and selects members on a case-by-case basis for each study.

5.1.3 Data Safety Monitoring Board (DSMB)

Certain studies also necessitate the constitution of a **Data Safety Monitoring Board** (DSMB). This is a formal, independent board of experts that advise on the safety and progression of a study. This includes the recruitment pace, planned interim analyses, and in some cases, futility analyses (i.e. to detect if a trial is likely not achieve its objectives). DSMB are needed for all research using an investigational product or interventions that entail potential risk to the participants or studies. DSMBs may also be required in research involving vulnerable populations, for example, pregnant women and children. The decision regarding the necessity of a DSMB for a study can be made by following international guidelines (National Institutes of Health (NIH), 1998) as well as the specific recommendations of the different relevant ERBs. DSMB members should be independent of the study. Membership should reflect a diverse range of expertise and include no fewer than three members, although five is most appropriate. A specific DSMB charter should be developed and put in place concerning the expectations and authority given to the DSMB. Depending on the specifics of the study, the Sponsor, Sponsor's representative, or Study Director convene the DSMB.

5.1.4 Data management plans, statistical analysis plans and monitoring plans

Each study should have a clearly identified data sharing plan (if relevant), **data management plan (DMP)** as well as a **statistical analysis plan (SAP)**. Depending on the complexity of the data and the analyses, either the protocol or stand-alone documents may contain the DMP and SAP. In the case of trials, the SAP should be a stand-alone document that is completed and validated prior to the enrollment of participants. The SAP may require amendments; documentation of these revisions should follow Epicentre guidelines. Irrespective of format, both documents should explicitly outline the procedures for data quality assurance.

Data quality assurances should encompass the entire study. This means that there should be clear indications of how data quality and study oversight is to be performed during the study. In some cases, this may include both internal and external monitoring (this is required for all trials of investigational products). This also includes describing in the analysis phase how the results will be validated. While ensuring the best quality data is a key component of all studies, there are different standards for analytic studies, interventional studies, and trials with implications for licensure of a new product. Standard guidance on the development of DMP and SAPs should be followed, and both validated and signed, prior to study enrollment.

In addition to the above, a monitoring plan should be put in place for each study. The primary goal of monitoring consists of ensuring adherence to standardized operation procedures, reporting and managing any deviations and violations, clear reporting of safety issues and providing feedback to the Study Director, Sponsor, DSMB and other bodies, which often include the ERB. Monitors execute the specific **monitoring plan** laid out by the Study Director, and/or Sponsor, and investigators. Monitors may be referred to by many different titles, such Clinical Research Associate, "on-site" monitor, "internal" monitor, "external monitor", Study Site Monitor and Quality Specialist. The number of clinical monitors depends on the scale and scope of the trial. The monitoring plan should assign clear roles and responsibilities as well as the hierarchical links between internal and external monitors. Depending on the nature of the study, the Study Director, Sponsor or Sponsor's Representative validate the monitoring plan.

5.1.5 Good Clinical Practices (GCP)

Additional specifications apply to a study adhering to Good Clinical Practices (GCP) and the protocol and accompanying study documents should include these details. GCP is a standard for research (usually investigational) that:

- Encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of studies;
- Ensures that studies are scientifically and ethically sound;
- Ensures proper documentation of the clinical properties of the product under investigation.

Studies conducted according to GCP are determined on a case-by-case basis. Although adherence to GCP requires meeting specific standards, all studies need to be conducted using good practices, irrespective of design or aim. Further to this, additional guidance on Good Participatory Practices (GPP) (UNAIDS, 2011) and Good Clinical Laboratory Practices (GCLP) (World Health Organization, 2009) may be applicable to certain studies.

Documentation in addition to the protocol may be needed in particular: Material Transfer Agreements if samples are to be collected, analyzed, and possibly shipped; Memorandum of Understanding or Research Collaborative Agreement if external partners are involved; proof of insurance for study participants.

5.2 Organization and oversight

Everyone named in the protocol should have a role and associated responsibilities, which can be easily identified in the text of the protocol. Table 2 provides an overview of key roles. Terminology may vary depending on the study type. Examples are provided below.

TABLE 2: ROLES AND RESPONSIBILITIES OF CONDUCTING INTERVENTIONAL STUDIES AT EPICENTRE

ROLES	KEY RESPONSIBILITIES
Study Director or **Sponsor or** **Sponsor's Representative**	Responsible for naming investigators and ensuring that any individual to whom a task is delegated is qualified by education, training, and experience to perform the delegated task. Possesses sufficient experience and qualifications for GCP compliant trials of investigational products (higher than for other trials). Assumes overall responsibility for the conduct of the study that includes but is not limited to: convening of the scientific committee and DSMB; validation of the protocol, SAP, decision to enroll participants, closure of databases and analyses; and assurance of appropriate monitoring.
Sponsor or Coordinating Institution	Bears ultimate responsibility for the integrity of the research. This is not to be confused with financing the research or assuming legal responsibility. Epicentre is often delegated the role of Sponsor by MSF or in some cases may act directly as the Sponsor. **It is important to note that the term Sponsor should only be used for studies of investigational products. The term Coordinating Institution should be used otherwise**.
Principle Investigator **Sponsor's Investigator or**	Responsible for direct daily oversight of the study; the Study Director (or otherwise named individual) delegates this task and any other tasks. Specific roles and responsibilities vary depending on each specific study,

ROLES	KEY RESPONSIBILITIES
Coordinating Principle Investigator	but general responsibilities may include: protocol writing, SOP oversight, supervision of site investigators, reporting, data analyses and other responsibilities.
Site Principal Investigator (PI) or Site Investigator	Bears responsibility for implementation of the study at a given site, including compliance, adherence to institutional policies, and observance of ethical principles. The site PI remains ultimately responsible for the day -to-day conduct of the study at his site, even when some aspects of the research are delegated to other members of the study team. They must personally participate in the project to a significant degree.
Co-Investigator	Devotes a specified percentage of time to the study. Co-investigators may also be responsible for specific scientific aspects of the study (e.g., data management and statistics, laboratory analyses, medical care). Must have an established and identifiable role in the study and devote a traceable percentage of their time. Coordination and facilitation are not sufficient to be a co-investigator, nor is institutional affiliation alone.
Other significant contributors	This includes individuals who contribute to the development or execution, but do not commit any specified, measurable time, to a project. They may be similar to co-investigators, but they actually do not have defined roles or responsibilities and are consulted as needed. These individuals facilitate the research and may help resolve specific issues.

A sample organigram is provided below (Figure 4) for a study which does not involve an investigational product. Each study will have a unique organigram and the terminology used should be adapted to each specific study.

The implementation of some trials can be complex and can involve large numbers of staff teams. The logistical and administrative aspects should not be neglected. When a trial is implemented in an MSF field, caution should be paid to ensure smooth collaboration between the staff of the MSF routine program and the trial staff.

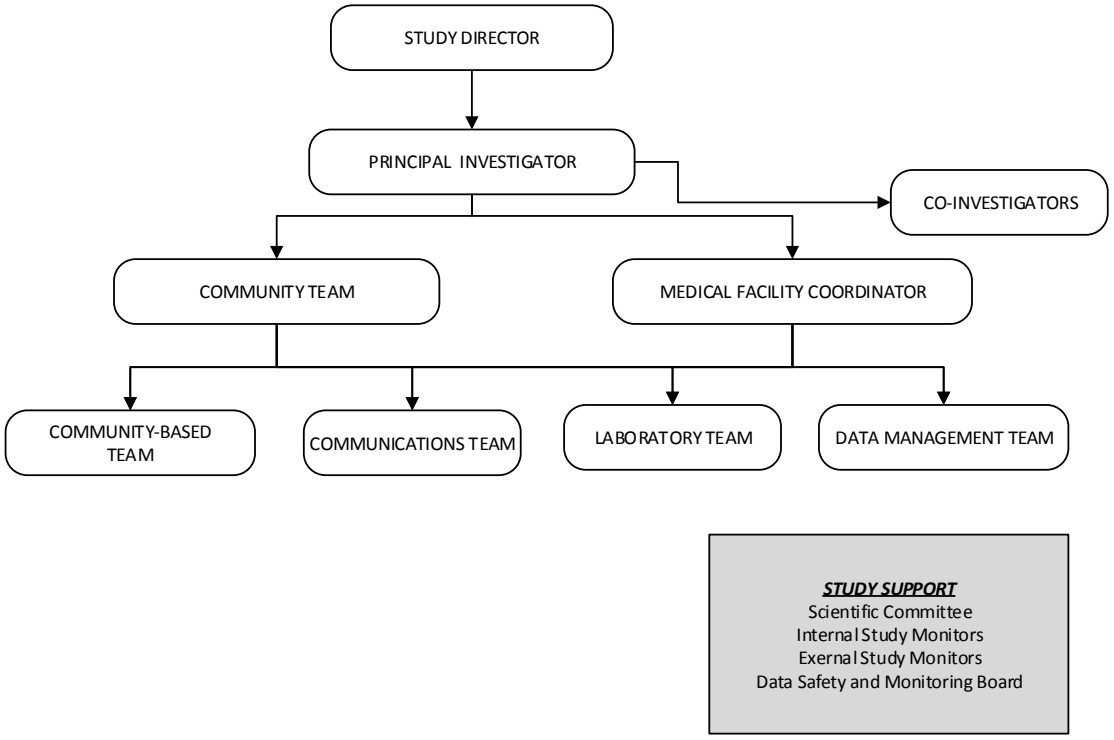

FIGURE 4: SAMPLE ORGANIGRAM FOR RESEARCH PROJECT

6 Misconduct

Scientific misconduct is not simply an academic exercise with consequences restricted to individuals. It can have repercussions for patients and populations. It can occur at all points in research and spans a wide range of areas. It is essential to recognize that misconduct can have a negative impact not just on a single individual or study, but also on the scientific reputation of the entire institution. Misconduct can entail issues with legal implications as well as other major concerns.

British physician Andrew Wakefield made a name for himself with a sensational 1998 paper claiming a link between vaccination and autism. Because of this paper, vaccination rates dropped throughout Great Britain and around the world, with the fraudulent link between vaccination and autism remaining prevalent today. When his paper was found to be largely composed of fabricated data, his medical license was revoked, and the paper retracted, but debunking this paper continues to be a concern in the world of vaccination. Examples of scientific career interrupted due to plagiarism, that can sometimes even be unintentional, are not uncommon.

Most cases of scientific misconduct are not as egregious as the two aforementioned; however, these examples demonstrate the potential far reaching effects and insidiousness of misconduct. Even on a minor scale, misconduct can have potentially grave consequences for the medical care of those in need and jeopardize future studies.

The term misconduct means intentional, knowing, or reckless, fraudulent behavior such as fabrication, falsification, plagiarism, or misrepresentation. It does not include honest errors or differences in interpretations (World Health Organization, 2017).

Concepts of scientific misconduct can be applied to all Epicentre's activities. The following activities that constitute misconduct are based on the WHO Code of Conduct for Responsible Research, as laid out in their policy for Handling Research Misconduct. These activities include, without being limited to, (World Health Organization, 2017):

- Data falsification or fabrication – the deliberate creation, recording, or reporting of false or fabricated data, including the manipulation or omission of data;
- Conducting research and field epidemiology in a manner which contravenes the terms of approval granted by relevant bodies (e.g., ERBs);
- Conducting research or field epidemiology for which Epicentre requires there to be prior approvals (e.g., from national authorities) whilst having failed to secure those approvals;
- Failure to follow procedures or exercise due care in order to avoid unreasonable risk or harm;
- Mismanagement or inadequate preservation of data and/or materials (e.g., biological samples);
- Misappropriation of data;
- Misrepresentation of interests, qualifications, or experience;
- Misrepresentation of involvement in a study or authorship on a publication (see 6.1);

- Failure to declare conflicts of interest;

- Plagiarism: The copying of ideas, data or text (or various combinations of the three) without authorization or acknowledgement. (See 6.2)

Misconduct can be considered distinct from poor practice, (addressed below) includes cases where there is suspicion that serious damage to individuals or populations may be at stake. It is also important to recognize that differentiating between the two is not always clear. Notably because Epicentre is not an health services provider (with some exceptions in Niger) and will thus almost always implement research project in a setting where other bodies are in charge of the participants health care such as MSF, the Ministry of Health or other partners. These differentiations do not negate the responsibility to ensure quality standard of care to study participants and try to reinforce care if needed

Misconduct differs from other forms of dubious or poor practices, which can range from inadequate data management and procedures, to negligence. Cases of poor practice can have serious health or moral consequences as well, but are more likely issues related to experience and integrity rather than purposeful misconduct (World Health Organization, 2017).

6.1 Misrepresentation

In addition to the above, another form of misconduct includes misrepresentation of the research study itself and its inherent limits. Although this could arguably constitute poor practice, it can also represent misconduct through misrepresentation. This means that the interpretation of the results of research depends on the design itself, as well as the strengths and limitations of a study. While a relatively rare event, the strongest evidence for interventions derives from a systematic review of multiple, randomized, blinded, placebo-controlled trials with allocation concealment and complete follow-up involving a homogeneous participant population and medical condition. Most research does not meet these criteria; this obliges those involved in a study to recognize and state, both in writing and in their representation of the study, the inherent biases and limitations of the research.

6.2 Plagiarism

Plagiarism is a frequent form of misconduct, but has different forms. Irrespective of the type of publication or presentation - report, journal article, protocol, proposal, concept note, oral presentation – ensuring ethical writing recognizes that the reader (or listener) assumes: the author(s) to be the originators and any "material, text, data, or ideas borrowed from others is clearly identified as such by established scholarly conventions, such as footnotes, block-indented text, and quotations marks" (Roig M, 2015). Plagiarism can, and often also occurs usually unintentionally, when there is a belief that an idea is "new", when in fact, upon closer inspection, it turns out not to be the case. This is referred to often as "rediscovery" (Roig M, 2015). A frequent example, in the effort to save time, reports and even protocols may be "recycled and adapted." It is important to recognize that plagiarism extends beyond peer-reviewed publications and extends to written and oral communications. This is the responsibility of the writer(s) and speaker(s) to appropriately acknowledge and verify sources and it requires careful attention to detail and verification.

7 Communication and dissemination of findings

We have a responsibility to communicate results. The expected outcomes of communicating and disseminating findings include:

1. To improve program outcomes in relation to medical care and prevention;
2. To assess the feasibility of new strategies or interventions; and
3. To advocate for policy change.

For each of these outcomes to occur, the knowledge gained from the conduct of research, operational research, and field epidemiology must be effectively communicated to the appropriate people that will use the information to inform action. It is useful to think of research and field epidemiology as tools for discovery, requiring translation into a form applicable to a target population and communication to populations in a meaningful and relevant way (Brownson et al., 2006). The final stage of the sharing of findings aims to improve health through long-term behavior change, program adoption, organizational change, or policy adoption—characterized in this simple schema below.

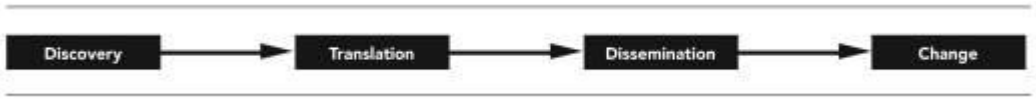

FIGURE 4: PATHWAY FOR TRANSLATION AND DISSEMINATION IN PUBLIC HEALTH (BROWNSON ET AL., 2006)

The obligation to communicate findings is ubiquitous, regardless of the size or nature of the activity or epidemiologic study. At minimum, participants and communities should be made aware of the results of the study or activity for which their data was used. This can be through community meetings, presentations, leaflets and other forms of communication appropriate to each context. Thereafter, the audience to whom the findings are made available will change, depending on the type of study conducted, the quality of the study, and the extent to which the results provide generalized knowledge.

Not all studies warrant publication in a peer-reviewed journal and publishing in a journal does not always target the most appropriate audience. The tools used for disseminating findings will depend on the type of study performed, the quality of the analysis, and the message intended for communication. This can take the form of a research report, descriptive paper, or targeted evaluation, a press release, a policy brief, or a publication in a peer-reviewed journal. For example, the communication of the results of outbreak investigations may best occur through press releases, while dissemination through a peer-reviewed journal may best suit a clinical trial.

7.1 Publication in peer-reviewed journals

Although there is a great deal of information available concerning the structure, format, and content of scientific publications, there is often little information on the more delicate issues of publication. Recent changes in the publishing industry, such as open access and predatory publishing, have resulted in sometimes questionable practices, further highlighting the need for an understanding of the publishing process beyond traditional technical requirements. It is important to highlight that Epicentre supports ensuring that articles appearing in peer-reviewed publications are available to individuals for free. For more information on the specific requirements for open access publication, guidance from Epicentre and MSF is available on this topic.

Scientific writing is demanding and can be a painful process. Accuracy, clarity, efficiency, and large amounts of often specialized information must be condensed into a short format. Authors should be able to synthesize evidence. This means the ability to know the scope and interpretation of existing evidence

and thereby place their work in context. Publications are only useful in so far as they provide readers with guidance on how the results of study can be used and how this information contributes to what is known.

Insufficient clarity and/or reduced accuracy can be unintentional, but this is not always the case. Ensuring research integrity requires avoiding questionable writing practices.

Whereas fabrication, falsification, and plagiarism are considered to be the "high crimes" of science, many other questionable practices frequently take place and these lesser crimes should command more attention (Zigmond and Fischer, 2002). Examples of lesser crimes in publication include (Roig, 2003):

- Data augmentation: Data that have already been published are published again with some additional new data.
- Data disaggregation: Data from a previously published study are published again minus some data points.
- Data segmentation (also known as "Salami Publication" or "Least Publishable Unit" or "Minimal Publishable Unit"): Data gathered by one research project is reported separately (wholly or in part) in multiple end publications.
- Reanalysis of the same data: The same data are reanalyzed. There are some instances when a new analytic technique can be used, but this is rare.
- Same data, different conclusions, by the same authors.

7.2 Authorship

Developing study communications with a team of people can be a challenging task, especially when contribution to the final product can be unequal. Issues relating to authorship are common in all types of scientific communications. While this section mainly deals with authorship of published studies, the principles herein apply to all reports and other types of documents where a team approach is used.

Writing a manuscript is a complex and demanding task. Even when roles and responsibilities are clear, scientific publications are often a source of friction. It can often be hard to decide who gets the credit and how much credit to give. Authorship represents an explicit way of assigning responsibility and giving credit for intellectual work, based on the honest contributions reflected in the final product. Some key aspects to consider are discussed below.

Who merits authorship?

To be a study author (see Uniform Requirements for Manuscripts; http://www.icmje.org):

- An author must have made a substantial contribution to all three of the criteria below:
    - At least one of following:
        - The conception or study design/method, e.g., conceived the research question, drafted the study protocol, critically reviewed and improved the methods; OR
        - Implementation of the study and acquisition of relevant data, e.g., coordination, training, follow-up, supervision, designed data collection forms, conducted/supervised data acquisition; OR
        - Analysis and interpretation of data; AND
    - An author should have drafted the article or revised it critically for important intellectual content; AND
    - Agreed on the contents of the final version of the manuscript and is able to explain the study accurately in their own words.

The following do NOT justify authorship on their own:

- Data collection or data entry without analysis
- Acquisition/provision of funding
- Provision of technical services (such as routine laboratory analysis, medical care to study participants), participants or patients, or materials.
- Providing ad-hoc advice on the study
- Participating as an investigator or a member of a steering committee on a study protocol
- Occupying a position of responsibility

While possibly essential to the work, these contributions do not justify authorship. These contributions can always be recognized in the acknowledgement section of a publication, if the contributors agree.

It is also important to note that Epicentre encourages the development of staff members from the country of implementation. As such, it is important here to make an effort to include individuals. This may require additional support, but is an important aspect of our work.

Who is designated as the first and senior author of the resulting journal article?

The Lead Epidemiologist or Principal Investigator (or otherwise named individual) should have a discussion with their supervisor (depending on the activity type) to determine who will assume the roles of first and senior (last) author of the manuscript. This should be done as early as possible in the process. In general, the first author writes the (first draft of the) manuscript and assumes responsibility for the integrity of the data and its analyses. The first author is usually the Lead Epidemiologist or Principal Investigator. The senior author assumes overall responsibility for the work and provides the final agreement on the contents of the manuscript. The senior author is also responsible for arbitrating any disputes between authors should they arise as well as ensuring that the article is taken through to completion (publication). In addition, either the first or senior author is usually the corresponding author. In all projects lead by Epicentre, the corresponding author should not be a short-term staff member.

The corresponding author bears responsibility for ensuring that all authors have read and agreed to the final submitted version of the manuscript. Epicentre should retain corresponding author rights to any study where Epicentre is first and last author.

Within Epicentre, there are **no "honorary" first or senior author positions**. In both cases, both individuals must be involved and assume responsibility for the research from inception to dissemination. As such, it would be disingenuous of someone to claim senior authorship status, if they have rarely fulfilled the first author role and are not equipped to respond to specific scientific and analytic questions. Similarly, writing the first draft of a manuscript is not sufficient to be the first author in some cases. The quality of the first draft and intellectual contribution are essential and if significant revision is required, this should be addressed by the senior author and responsible Director.

How should the rest of the authorship order be determined?

For the remaining authors, no universally accepted protocol for order exists. Although there are no hard and fast, or even simple rules, there are several points to keep in mind:

- Authors can be listed in decreasing order of their contribution, or in keeping with the journal's guidelines.

- Consider group authorship if there are large amounts of disagreement or consider alphabetical authorship if there is a problem with order. If there is a large amount of disagreement concerning author order, this is often the result of poor management of the paper by the first author or lack of adequate supervision by the last author.
- Some individuals prefer to use an asterisk (*) to denote that several authors contributed equally. This may be a “peace-making” tool, but it is important to remember here that when papers are indexed, these asterisks usually do not appear, and some journals do not allow this classification.

Any agreement reached regarding authorship should, ideally, be established as early as possible in the development of the project/study. The publication plan should incorporate sufficient flexibility to account for changing roles and responsibilities. Sometimes an individual not initially designated as an author makes substantive contributions and subsequently earns a place on the author list. Likewise, an individual previously designated as an author fails to carry out their tasks, making their contributions not sufficient or important enough to merit authorship (or requiring a change of their place in the order of authors). The number of authors should be commensurate with the work itself. Both too many, and too few, authors may indicate a problem.

Another delicate situation includes when authors require extensive assistance with their writing. One example would be when a staff member relies heavily on another individual to make substantial editorial changes to the writing of the manuscript, not just copy-editing or language correction. These individuals may, or may not, be acknowledged. Failing to note the use of an editor in the acknowledgements, or not including the editor as an author, is misleading and is a form of misrepresentation. The issue of authorship can become highly politicized. Misrepresentation of author contributions is a serious matter and represents a form of misconduct, as mentioned in the previous section.

All the above mentioned authorship rules (as well as misinterpretation and plagiarism) also apply to oral and poster communication in conferences or in any other places where an epidemiologist represents Epicentre.

8 Key points

The aim of this document is to improve understanding of epidemiologic terms, concepts, and required skills for field epidemiology and research at Epicentre.

A distinction between field epidemiology, observational studies and interventional studies is required for practical reasons and ethical requirements.

Definitions

- Field epidemiology serves the core function of understanding the ongoing health events in a population. It provides an evidence base for programmatic goal setting, and can inform research agendas for more detailed epidemiologic analyses.
- Observational studies rely on observation only and use both descriptive and analytic approaches to answer questions affecting program implementation.
- Interventional studies require a formal hypothesis with allocation of exposure.

Study design and epidemiologic approaches

- Epidemiologic studies and activities can be classified according to whether there is assignment of an exposure, random allocation to groups, and the testing of a hypothesis.
- Not all Epicentre's activities are research.
- Field epidemiology mainly requires observational, non-hypothesis testing approaches.
- Observational research mainly uses observational, descriptive study designs and methodologies. It sometimes requires observational, analytic designs, if testing a hypothesis.
- Interventional research employs interventional study designs to test a hypothesis related to an assigned exposure, which may or may not require random allocation of participants to groups.
- Qualitative study methodologies are important to understanding issues and answers questions that are not, or not satisfactorily, amenable to quantification.

Practical guidance

- All Epicentre activities, whether classified as field epidemiology, observational studies or interventional studies, require adherence to general practical guidelines for design, documentation, implementation, and dissemination.
- Appropriate documentation and oversight differs in content, but conceptually must comply with institutional standards.
- The requirements for ethical review exceptions should be determined on a case-by-case basis.

Obligations

- Whether performing field epidemiology, observational studies, or interventional studies, it is expected that the activities will be performed with care for scientific rigor, minimizing harm and maximizing the benefits for participants.
- Misconduct is applicable to all field epidemiology and research.
- The communication and dissemination of findings are mandatory step for all activities.
- As a general rule, high standard of professional ethics is expected to ensure the respect of study participants.

9 Additional terms

The definitions below are taken from various sources.

Anonymous: Anonymous data and samples are never labelled with identifiers or codes. No one, not even the researcher, can connect these to the individual who provided it.

Anonymized or De-linked data: Data originally collected with identifiers or codes, which subsequently have been removed, are de-linked or anonymized. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). This prevents study participant re-identification (ICH Expert Working Group, 2007).

Assignment: The process in a study where the researcher allocates participants to two or more groups, trying to produce groups as identical as possible to allow for a valid comparison of the results. Matching and random assignment are the two most common methods.

Audit of a trial: A systematic examination, carried out independently of those directly involved in the clinical trial.

Baseline: In an intervention study, a phase during which the participants have not received any intervention. Often within MSF, the term is used to refer to a survey carried out at the start of a field program or intervention to as a basis for assessment.

Before-and-after study: A method of control in which results from experimental subjects are compared with outcomes from patients treated before the new intervention was available. These are also called historic controls.

Beneficence: An ethical principle implying that every effort should be made to maximize the benefits to participants.

Bias: If the study sample is not representative of the population, the inference made from the result may be misleading. There are many different types of bias.

Blinding: A controlled trial may be blinded if participants in the trial are likely to change their behavior in a systematic way that may influence the outcome of the study if aware of the intervention they receive. The term “masking” is sometimes used instead of “blinding”. Studies may be single, double or triple blinded.

Cohort study: The term used to describe a longitudinal, observational study that collects data on exposures over time, and then compares the occurrence of a condition between groups with and without a given exposure.

Cost–benefit analysis: A type of economic study design in which both costs and benefits of interventions are expressed in monetary units, allowing direct comparison of competing interventions.

Cost–effectiveness analysis: A type of economic study design in which the net monetary costs of a health care intervention per unit measure of the clinical outcome's effectiveness allows direct comparison of competing interventions.

Crossover study: A special design of controlled trials in which half of the participants are randomly assigned to start with the placebo/best available standard treatment and then to switch to active/experimental treatment, while the other half does the opposite.

Cross-sectional study: An observational study design in which measurements are made on a single point in time.

Descriptive study: An observational study that simply describes the distribution of a characteristic.

Distributive justice: An ethical principle implying that participation in the research should correlate with expected benefits. No population group should carry an undue burden of research for the benefit of another group.

Duplicate or redundant publication: Publication of a paper that overlaps substantially with one already published by the same authors.

Efficacy: The extent to which an intervention, procedure, regimen, or service produces a beneficial result under ideal conditions (trial conditions). Ideally, the determination of efficacy is based on the results of a randomized controlled trial. Efficacy answers the question: "Does it work?".

Effectiveness: A measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field under usual circumstances, does what it is intended to do, for a specified population. Effectiveness answers the question: "Is there a benefit?".

Intervention study: A study design in which the investigators test the effect of an intervention.

External validity: The extent to which the results of a study sample may be generalized to the population from which the sample was withdrawn; also called generalizability.

Good clinical practice (GCP): A standard for research (usually investigational) which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting, and documentation of studies, and which ensures that studies are scientifically and ethically sound and that the clinical properties of the product under investigation are properly documented.

Hawthorne effect: An effect that results in the improvement of participants' performances through being observed and/or social contact.

Health systems research: Studies of the health system as a whole (or one of its building blocks). It can address a wide range of questions, from health financing, governance, and policy, to problems with structuring, planning, management, human resources, service delivery, referral, and quality of care in the public and private sector. It is often highly multidisciplinary, with a strong emphasis on social sciences, economics, and anthropological investigations (e.g., community perceptions of health care). (Remme et al., 2010).

Implementation research. Implementation research constitutes a systematic approach to understanding and addressing barriers to the implementation of effective, quality health interventions, strategies, and policies. A range of stakeholders, such as healthcare practitioners, policy-makers, researchers, and community members, drive this research. Stakeholders all work together to frame the research questions based on local needs, conduct the study, and implement the results (Remme et al., 2010).

Inference: A generalization made about a population from the study of a subset or sample of that population.

Informed consent: An ethical requirement for participation in a study, indicating that a competent person, in possession of all the relevant information, freely agrees to participate.

Internal validity: The degree to which the investigator's conclusions correctly describe what actually happened in a study. It means that within the confines of a study, results appear to be accurate, the methods and analysis used stand up to scrutiny, and the interpretations drawn by the investigators appear supported.

Literature: Reports of previous research done in an area under study.

Matching: A sampling method to ensure that two groups to be compared have similar characteristics. In an intervention study, pairs of similar "matched" subjects are formed, and then one member of the pair is (randomly) assigned to one group, and the other member to the other group.

Meta-analysis: A methodology to critically review research studies and statistically combine their data to help answer questions that are beyond the statistical power of single studies.

Monitoring (in GCP): The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Multicenter trial: A trial conducted according to a single protocol at more than one site, and, therefore, carried out by more than one investigator. These site-specific investigators are referred to as Site-Investigators or Site-Principal Investigators. In Niger for example, Epicentre may conduct single-center, multi-site trials. In this case, there is one central PI and site-specific investigators responsible for each of the study sites.

Non-nominal linked information: Information linked to a person by a code (not including a personal identifier) and known only to the investigator(s).

Null hypothesis: In scientific methodology, we do not test the research hypothesis directly. Instead, we start with an assumption that there is no difference or association between the variables compared. This is called the null hypothesis (H0). If statistical analysis rejects the null hypothesis, it means that the alternative hypothesis is probably true, and that there a difference between the group or a relationship between the variables.

Objectivity: Objective measures are made in a process involving a minimum amount of human interpretation, for example measurement of height.

Observational study: A study design in which the investigators observe and record events taking place in the study.

Peer-reviewed journal: A journal in which the articles are vetted by independent referees for quality and interest.

Pilot study: A preliminary study to test the feasibility of the protocol, before implementing the study proper. A pilot study is not the same as a "pre-test" of study materials (questionnaires, procedures, and other documents) that is necessary in every activity.

Population: An entire set of persons, animals, objects, or events which a researcher intends to study.

Power: A statistic indicating the probability of rejecting the null hypothesis when the alternative hypothesis is true. Statistical power of a study is thus the probability of observing an effect (of a specified effect size) if one exists.

Protocol: The detailed written plan of the study.

Quality assurance: A system to ensure that the study is performed and the data are generated, recorded, and reported in compliance with the protocol, Good Clinical Practice, and relevant regulations.

Qualitative methods: A research approach that emphasizes non-numerical data and interpretive analysis.

Quantitative methods: A research approach that emphasizes the collection of numerical data or data that can be quantified.

Questionnaire: A means of collecting data from people where they provide responses to a set of questions, either in their own words (open-ended questions), or by selecting from among pre-defined answers (closed response questions).

Randomized controlled trials: Intervention studies characterized by the prospective assignment of subjects, through a random method, into (at least) an experimental group and a control group.

Retrospective study: An observational study design in which the investigators study past events.

Rosenthal effect: The phenomenon in which the expectations of researchers in a study influence the outcome.

Sample: A subset selected for a study from a larger population.

Subjective measures: Measures involving a substantial degree of human interpretation, for example ratings of pain.

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