

# Responsible Epidemiologic Research Practice (RERP)

## A guideline developed by the RERP working group of the Dutch Society for Epidemiology

### Background

There is ample evidence that scientific research practices are not sound and that study results are not as reproducible as they should be.<sup>1,2,3</sup> Evidence indicates that questionable research practices (QRPs) in fact are quite common.<sup>4-7</sup> QRPs are often of a methodological nature and may for instance concern selective reporting of research findings, not reporting the results of a scientific study, protocol deviations not clearly described in the publication, data dredging, and presenting a study as being of hypothesis testing nature although it was set up as an explorative endeavor. A number of cases of research fraud and misconduct served as a wake-up call for the scientific community.<sup>4,8,9</sup> In a meta-analysis of 21 surveys Fanelli reported that 33% of the scientists admitted to having been involved in QRP at least once in the last 3 years.<sup>4</sup> Research integrity is a topic that is receiving more and more attention.<sup>10,11</sup> Concerns about research misconduct (RM) such as fabrication or falsification of data and QRP have triggered the establishment of several codes of research conduct including for example, the Netherlands Code of Conduct for Scientific Practice<sup>12</sup> the European Code of Conduct for Research Integrity<sup>13</sup> and the Singapore statement on Research Integrity.<sup>14</sup> Furthermore the US National Academy of Sciences has published a report on being a scientist and on how it expects scientists to operate.<sup>15</sup>

Concerns about QRP and RM clearly also apply to biomedical research and by extension to epidemiologic research. A few years ago a series of articles in the January 2014 issue of the *Lancet* voiced concern about how biomedical research is conducted and proposed measures to improve research practice. In the associated commentary, Kleinert and Horton recommended researchers to reconsider how they conduct their studies and how they can contribute to reliable and accessible evidence that addresses the challenges faced by society.<sup>16</sup> In their REWARD (Reducing Waste and Reward Diligence) statement of 2014, also published in *Lancet*, the research waste campaign has set a number of objectives to maximize our research potential (<http://www.thelancet.com/campaigns/efficiency>). In 2009 Glasziou and Chalmers estimated that 85% of today's clinical research may be wasted, not contributing to the advancement of science.<sup>17</sup> In a more recent (2016) series of articles in the *Journal of Clinical Epidemiology* the need for more transparency and accountability in biomedical research was further emphasized.<sup>18,19</sup>

Concern about QRP in epidemiology is not new. In 1988 the late Alvan Feinstein already described how fraud and deception cause prominent problems in the world of medicine.<sup>20</sup> In 1991 a report on Good Epidemiological Practice was published, providing guidelines on how epidemiologic research in occupational and environmental epidemiology should be conducted.<sup>21</sup> This report already contained elements of responsible epidemiological research practice. Concern about selective reporting, or outcome reporting bias has been greatest in the field of clinical trials, where most evidence on the occurrence of the QRPs has been generated. Currently preregistration of trials for example at the US Government trials register is quite common but still

not universally accepted.<sup>7</sup> The All Trials initiative has played a key role in getting preregistration anchored into the legislative framework of the United Kingdom.<sup>22</sup>

Epidemiologic research has had and is likely to continue to have an important role in evidence based public health and clinical medicine. Epidemiologic research findings have greatly contributed to improving human health by identifying risk factors, evaluating preventive programs, determining the best treatments for disease and care, and providing insight in prognostic factors. Given the limited resources available it is of great importance that biomedical research is carried out according to the best feasible scientific standards. Many epidemiologic studies cannot be done without the participation of patients or healthy volunteers who invest their time and participate in studies they believe are performed according to the highest feasible standards. Scientists have a responsibility towards these human subjects to collect, analyze and report these data, following responsible research practices. Although much has already been achieved in the form of the three codes mentioned above, trials registration and other reporting guidelines (see Equator website: [www.equator-network.org](http://www.equator-network.org)), much work still needs to be done.

Epidemiologists often are perceived and also see themselves as the sentinels of the methods for applied clinical and public health research. They often participate in multidisciplinary studies because of their valued knowledge and skills with respect to research methodology. Therefore they often are in good position to advocate responsible research practices far beyond their own discipline and have the opportunity to set an example for other research fields as well.

The concerns mentioned above have led the Dutch Society of Epidemiology (VvE) to set up the working group Responsible Epidemiologic Research Practice (RERP) to address this issue. This RERP working group has developed a guideline about how epidemiologic research should be conducted in order to increase value and reduce waste in epidemiologic research and increase transparency and accountability. The VvE has a 30-year track record of activities to increase the value of epidemiologic research and training, including the certification of epidemiologists at MSc and PhD level. The reputation of Dutch epidemiologists, and of scientists in general is still high and the VvE is keen on maintaining this. The society therefore encourages its members and other epidemiologists to inform themselves of this document and follow its recommendations. So far the Dutch epidemiologic research community has remained relatively void of identified fraud cases, but a few of these may ruin this high standing reputation. More importantly, epidemiologic research should meet high quality standards, should be reproducible and should always be relevant to society.

### **How RERP was developed**

In their five year strategic plan for 2016-2020 the VvE identified improving the quality of epidemiologic research as one of its key objectives. The RERP working group reviewed recent publications such as the earlier mentioned series in the Lancet on research waste and Responsible Research Practice but also earlier publications. The working group held several face to face meetings to review various draft proposals for the RERP guideline. In constructing the guideline it essentially followed the evidence based methodology to develop guidelines, the Evidence Based Richtlijn Ontwikkeling or EBRO method.<sup>23</sup> As recommended in EBRO the working group consulted epidemiologists to obtain their input and to assess their support for the guideline. The working group did not follow the EBRO recommendation to conduct a systematic review of the

literature on research practice, this was not seen as a key objective. The literature search conducted did not yield any evidence, in support or against, that a guideline to enhance responsible research practice, or components thereof would be effective. A draft RERP proposal was circulated among the approximately 1100 members of the VvE and they were invited to provide comments. A preconference to the 2016 annual Dutch conference of the VvE, the WEON (Werkgroep Epidemiologisch Onderzoek Nederland), was organized in which the RERP proposal was discussed and later amended. The final draft was sent to all VvE members with the request for final commenting in March 2017.

## **The RERP guideline**

As stated earlier, several national and international institutions in the scientific community have published codes of conduct for researchers.<sup>12-14</sup> These codes of conduct are aspirational in the sense that they focus on virtues and values, and provide general guidance for the way scientific research should be conducted. All three codes prescribe that scientists should be reliable, impartial, independent, honest, objective and open. These principles need to be translated into concrete behavior and expressed in terms of do's and don'ts. By applying the general principles laid down in these codes to the entire sequence of an epidemiologic study the working group developed the RERP guideline.

As in many other research, in a typical epidemiologic study three phases can be identified. First the study must be prepared. Second, the study is conducted or executed, and third, the study findings are published and the study is archived. This boils down to the following sequence:

1. Preparation of the study
  - a. Setting up the study group
  - b. Constructing a meaningful research question
  - c. Designing a study protocol/grant proposal
  - d. Submitting a grant proposal and obtaining financial support
  - e. Ethical review
2. Conducting the study
  - a. Human volunteers protection
  - b. Data collection
  - c. Statistical analysis
  - d. Preparing report(s)
3. Dissemination and after-care
  - a. Manuscript submission and reporting
  - b. Contact with journalists
  - c. Data archiving and sharing
  - d. Document archiving
  - e. Accountability and transparency

RERP applies to all of these elements and beyond. The level of detail in documents to be archived should be such that a knowledgeable scientist can reconstruct how the study was conducted and why certain decisions were made. The more details provided the more

transparency is achieved and the better accountable the researchers are. We will now describe in general terms how to do so, following the general sequence of any epidemiologic study.

## **1. Study preparation**

### **1.a- Setting up the study group**

*The first step in any epidemiologic study is establishing the study group.* Scientific research is preferably not conducted in solitude, but by a study group in which scientists work together to collectively design, conduct and report the study. Study groups as a rule are more self-corrective than researchers working by themselves.

The study group should contain sufficient expertise to be able to reliably carry out the entire study throughout all its phases and aspects. Members of the study group should be sufficiently trained to fulfill the tasks they will be accountable for. Each member should be aware what he/she is expected to contribute and what tasks must be performed. It is strongly recommended that at this stage author lists are made for the envisioned publications. In order to avoid disagreement at a later stage it is recommended to determine the order of authors, together with their responsibilities. Authors should only be added if they fulfill the relevant criteria for authorship as for example described by the International Committee of Medical Journal Editors.<sup>24</sup> Conversely, authors who do not perform the tasks as agreed should be removed from the author list. This should be evaluated before manuscript submission. Also, potential conflicts of interest and financial aspects should be discussed within the study group at this stage and the way these will be handled.

### **1.b- Constructing a meaningful and relevant research question**

Any sound and reliable scientific study needs to be carefully designed and planned. *The first task of the study group is to define the aim of the study, or the specific hypothesis or research question to be tested.* A thorough systematic review of the existing literature on the study topic should form the basis of the decision whether to conduct a certain study. Chalmers et al recommend that any study proposal should include a systematic review of the literature to justify the need for this new study.<sup>25</sup> Researchers should take into account what is already known on a certain topic, what their proposed research will add and to what societal expense this new knowledge can be generated. The preferred method to summarize what is already known is by means of a systematic review. If evidence is sparse such an approach can be too sophisticated, but the study group should convince itself that they have a good understanding and knowledge of the available evidence.

Researchers should start documenting their work from this phase onward, so they can later disclose how they have derived their definitive research question.

### **1.c- Designing a research grant proposal and the study protocol**

*Every epidemiologic study, with the aim of publishing the results should be based on a detailed research protocol describing the study. The level of detail should be such that another study group would be able to carry out the study as intended with the protocol in hand.* It is the responsibility of the entire study group to produce the research grant proposal and the study protocol.

A grant proposal can serve as study protocol if it has the necessary level of detail required for a study protocol. Grant proposals are intended to obtain the necessary resources for a study and may not yet describe the planned study in all its relevant details and finesse. In that case the study group will have to prepare a detailed study protocol prior to starting the study as soon as funding is obtained.

The study group should ensure that adequate research methods are used. These methods should meet the standards of the research field. Research using suboptimal research methods is considered unethical and adds to the body of research waste. Before the study group starts conducting the study a protocol should be written and agreed upon. Ideally the protocol contains a description of the research design, justification of the study population and sample size, a data management plan with quality assurance and auditing steps, and the statistical analysis plan. It should also contain a list of envisioned publications and authors who will contribute to each publication. *Once final it is strongly recommended that the study protocol is made public, either by placing it on a publicly accessible website or by uploading it in an appropriate studies register. Prepublication of the protocol strongly enhances transparency and future accountability.* There might be occasions where the study group decides not to disclose a study protocol prior to publication of the study results, for example the development of a new drug or medical treatment, or innovative discovery. In such cases a copy of the protocol should be deposited with a reliable person or institution that will treat it as confidential until the study is completed, for example a notary. Then, once the study is completed the deposited copy can be disclosed.

#### **1.d- Submitting a grant proposal and accepting financial support**

The entire study group is responsible and accountable for the contents of the grant proposal and no promises should be made to the funding institution that will be difficult to keep, without mentioning this. Members of the study group should not be involved in the review of the grant proposal. In addition, members of the study group should disclose at this stage any other sources of funding received or conflicts of interest that may collide with the funding sought.

On the other hand, the study group should only accept funding if an independent execution of the entire study, including full disclosure of the results, without any interference of the sponsor is guaranteed. No publication vetoes are acceptable and stopping rules should be formulated carefully. It is acceptable that the sponsor may claim the right to see the results prior to disclosure and have a reasonable embargo period, but it should not be in the position to unreasonably delay or block publication or influence how the results are disclosed.

#### **1.e- Ethical review**

Epidemiologic studies involving human subjects are required to be reviewed by an appropriate ethical review committee. Ethical review must be fully obtained prior to the start of data collection. In most Western countries all intervention studies on human subjects must be reviewed by a certified ethical committee. Observational studies on humans may not necessarily be reviewed by an ethical committee, but we recommend the study group to verify the need for review with the ethical review committee. In the case review is not necessary, a waiver must be obtained.

## **2. Conducting the study**

*The epidemiologic study should be carried out in accordance with the study protocol. Protocol deviations should be recorded and reported with the reasons why these were deemed necessary. Alternatively the protocol can be amended, but these amendments must be reported.*

### **2.a- Human volunteers protection**

In case the epidemiology study includes human volunteers the internationally accepted guidelines should be followed (see e.g. declaration of Helsinki <sup>26</sup>). Human volunteers should be well informed about the study and about what is asked from them and should all sign an informed consent form that should be archived in the study records. Risks and burden should be clearly explained. Risks and burdens should be acceptable and proportional to the potential benefits of the study. Human volunteers should be treated with respect and their privacy should be well guarded. Human volunteers are protected by law and legal rules and regulations must be adhered to.

### **2.b- Data collection**

The data collection phase should also be carried out in accordance to the protocol. Protocol deviations should be documented, reported and motivated. Quality checks and checks for completeness should be included. Datasets should be checked for accuracy by means of manual checks and by running frequency tables and cross tabulations to identify errors. Copies should be stored in secure places. *The data collection process is a vital element of any study and therefore should be documented in detail.* A digital log, analogous to the lab journal in laboratories should be part of this documentation process.

### **2.c- Statistical analysis**

Prior to the statistical analysis the raw dataset should be finalized. No changes to the raw dataset should be made once the statistical analysis has started. Again, *the statistical analysis should be conducted according to the protocol.* Often additional analyses will be conducted that were not foreseen at the time of protocol development. These should be designated as such in the report. Journal reviewers may request additional analyses. It is obvious these are not foreseen in the study protocol and if these are done it must be mentioned they were included following requests by the reviewer.

Protocol adherence should not be that rigorous that the data are not optimally analyzed. On the other hand, planned but not conducted analyses, should also be reported and decisions motivated.

The syntax files of all conducted analyses should be stored as key document and archived.

### **2.d- Preparing report(s)**

Preparation of the report is a responsibility of the entire study group. *The report must be an accurate, balanced and concise reflection of the conducted study, taking into account existing guidelines and it should describe its limitations and any deviations from the protocol.* The report

can be in the form of one or more scientific publications. Explorative analyses must be identified as such in the publications.

### **3.- Dissemination and archiving**

*A scientific study is only completed when all its results are properly reported and disclosed and when the study has been well documented and archived.* Documentation and archiving should be done in such a way that a trained scientist, not necessarily an epidemiologist, can reconstruct how the study was conducted. Ideally the report(s) on its own must fully document the conducted study, but in most cases it will not contain every detail of the study. All epidemiologic research with the aim of publishing it should be based on a detailed study protocol. Caution should be taken in publishing results from non-protocolled research in order to avoid publication bias and outcome reporting bias. As an exception non-protocolled research can be published, under the condition that this is clearly stated in the publication. In addition, explorative research, in which multiple analyses are conducted is regarded as publishable, under the condition that this is clearly stated in the methods section and clearly pointed out in the discussion section and abstract.

#### **3.a Manuscript submission and reporting**

Editorial instructions must be followed when submitting a manuscript for publication. Conflicts of interest must always be disclosed in the publication.

There is no objection to writing multiple manuscripts about a study as long as the content is distinctively different and this is not aimed at merely publishing as many reports as possible. If the multitude of results require to write several publications, they should within reason be cross-referenced so readers are aware of other publications. The contributions to the manuscript of all authors must be as described in the protocol.

*Any protocolled study must be published.* In the unlikely situation that no scientific journal is willing to accept the manuscript it should be disclosed at the website of the responsible institution and if applicable the register where the study was pre-registered or in any other form that is publicly accessible. In case of a study remaining unpublished it is very important to document the trail of manuscript submissions and other circumstantial reasons for not publishing the results.

#### **3.b- Contact with media**

Contacts with journalists are an optional part of the dissemination process, after the reviewed manuscript has been accepted for publication and preferably published. *The study and its results should be presented to journalists in a reliable and balanced manner, without making the results appear to be more (or less) than they really are.* Authors should take efforts to ensure that the text to be published in the journalistic product is accurate, precise, correct and understandable for the readers.

#### **3.c- Data archiving and data sharing**



*Once the report is in a final form, the study group must ensure that the raw data files and the final dataset used for the statistical analysis are securely stored, protecting privacy of subjects and accompanied by a fully explanatory data description or code book.*

*Data sharing in principle is encouraged and should be the norm, since re-use of data makes research more cost-effective.* However, this secondary use should be in accordance with the RERP guidelines.

Most sponsors do not specify ownership of the data. In that case the study group must consider itself (or more formally the institution) as the owner of the data, with all the benefits but also all the responsibilities of good ownership. If a sponsor insists on data being owned by them, the study group must consider refraining from the grant if external ownership is deemed incompatible with the standards of the study group. Research data should only be shared for re-use if the secondary analyses are compatible with the approval obtained from the ethical review committee. In case of doubt this committee should be asked to review the request for data sharing. In this respect we refer to findable, accessible, interoperable and re-usable (FAIR) guiding principles for scientific data management and stewardship (<https://www.ncbi.nlm.nih.gov/pubmed/26978244>)

### **3.d- Document archiving**

A study consists of more documents than the protocol, the dataset, statistical analysis, syntax, results and final report(s). For transparency and accountability reasons it is recommended that other documents, such as questionnaires, meeting minutes, conference presentations, interim reports etc. are also stored for future reference. As example of a storage facility we refer the reader to “Dataverse”, which has been set up by an international community of academic institutions to store datasets, syntaxes etc.<sup>27</sup> This facility is access controlled. Researchers can choose the level of access preferred. Another example is DANS, the Dutch network of data storage for academic institutions The data and codebook are not sufficient to describe the study.

Which documents should be archived? As a general rule archiving should be such that a well-trained scientist, not necessarily an epidemiologist will be able to reconstruct in detail how the study was conducted and also be able to repeat the study. The archive must also contain all relevant details for an investigation or an audit that may be requested by a scientific journal or a committee investigating an allegation of a breach of research integrity. The box below, containing the key products or “deliverables” produced in the earlier described elements of the epidemiologic study that should be stored in the archive.

<b>Study element</b>	<b>Deliverable</b>
1a. the study group	Minutes of the relevant meetings
1b. meaningful research question	A statement describing the study hypothesis and/or study objective

1c.research protocol/grant proposal	Copy of protocol and/or grant application, with sufficient detail to enable a trained scientist to reconstruct the entire study
1d.grant submission	Agreement with funding agency and terms of conditions
1.e ethical review	Copy of the ethical committee approval if required
2a.human volunteers protection	Informed consent and Informed Patient information
2b.data collection	Raw database, code book, data collection log
2c. statistical analysis	Syntax, program files
2d. report preparation	Final report, as intended for submission to contractor and or journal and a copy of the publication(s)
3a.manuscript submission and reporting	Correspondence with editors
3b. contacts with media	Press release or similar documents and the media coverage
3c. data archiving and sharing	Documents and agreements with third parties who obtained access to the data
3d.document archiving	Index of archived documents and files

### **3.e- Accountability and transparency**

*Throughout the study execution, but also after the study has been finalized, the study group is accountable for its work.* Requests from third parties to explain and elucidate the study should be taken seriously and – within reason - complied to. The task of being a corresponding author of a publication comes with the responsibility to answer questions from interested parties, within a certain limit of reason. Issues arising from the conduct of the study, in which the study group is held accountable should also be dealt with accordingly. Accountability of study group members is not restricted to their own individual contribution. It encompasses the contributions of the other members as well. In case of concern about RM or QRP by a member of the study group, noticed by another member proper action should be taken, for example by discussing this with the entire study group or even by reporting this to the appropriate Research Integrity Authority.



## Discussion

Responsible research conduct and scientific integrity are topics that are receiving increasing attention in the lay press as well as in the scientific literature. The VvE has developed the RERP guideline with the aim to make our membership and other researchers further aware of these key issues. We hope epidemiologists and scientists in other disciplines will embrace our guideline and start practicing it in their day-to-day work as responsible researchers. We realize that implementation of these guidelines will cost some effort, both to convince colleagues of the need as well as to set up the infrastructure and training to adhere to these guidelines. Following the guideline during the conduct of an epidemiologic study should not lead to an unreasonable increase in additional workload of administrative tasks. It would be helpful if a software program can be developed that assists the study group during the conduct of the study and provides reminders and solutions for all the elements and steps involved. Some research institutes already have software in place intended to aid researchers with their projects. At the preconference several were mentioned: Some institutes like NIVEL (Netherlands Institute for Health Services Research) have developed standard operating procedures to be followed for research following specific designs. They also developed an ISO certified quality management system covering all aspects of conducted research. Several universities or university departments (Groningen and Nijmegen) have software in place where critical documents of studies can be deposited.

RERP should not result in a box ticking exercise. It should assist the study group in documenting and archiving the study and it should increase transparency and accountability. Furthermore RERP should not be considered the single solution to QRP. More is needed, especially a cultural change in research institutions and among scientists is needed, with less focus on output quantity, impact factors and career development but more on responsible research conduct.

Epidemiologists should be more open and frank about their research. They should welcome intervision and critical remarks from their peers. We strongly believe that the basis of this cultural change lies in educating epidemiologists and also by implementing RERP in the curriculum of epidemiology courses.

The main responsibility of implementing and enforcing the RERP guideline does not lie with the VvE, but rather with the individual epidemiologist, the department he/she works in and ultimately with the employer. One should realize that QRP or RM by one individual epidemiologist can adversely impact the reputation of the institution and eventually to the epidemiology community as a whole. This also applies to the sponsor. Sponsors are encouraged to more closely follow and audit projects that receive funding. They have an obligation that the funding is well spent and that the study is conducted according to the funded project proposal. The VvE welcomes recent requirements of several Dutch funding agencies that require researchers to use data management software to ensure quality and documentation. The RERP guideline is a first step but not the final one towards enhancing responsible research practice. It can be expected that future developments will require the VvE to update this document and further review its contents. RERP requires more extensive documentation and archiving than before. Some documents are strongly

recommended to be disclosed on the internet prior to data collection, including the study protocol. Researchers should be aware that due to this improved documentation and disclosure the privacy of study participants can become at risk. Sharing data is a virtue, but researchers must be aware of the importance to protect the privacy of the study participants. Principally data sharing is seen as a responsible practice since it makes better use of the limited resources and thus is further encouraged. However, also data sharing is not without responsibility. The data provider should ensure that the data are used properly and that the data receiver understands the data and uses it in a scientifically responsible way. Co-authorship also comes with the responsibility to ensure proper data use and interpretation.

The results of epidemiologic research should be available to all. Therefore open access publishing is supported. However it should not be at the expense of the peer review process. Certain open access journals can increase their profits by publishing as many manuscripts as possible. This will have a negative impact on the quality of the published articles.

In the long run we are convinced RERP will demonstrate its merits by means of creating a more transparent and better documented process. We have formulated a set of recommendations to our members, that have been taken from our document and are displayed in the box below:

### Set of recommendations

Study element	Recommendation
1a. the study group	The first step in any epidemiologic study is to establish a study group and the responsibilities and accountabilities of its members.
1b. meaningful research question	The first task of the study group is to define the aim of the study, or specific hypothesis to be tested. Include a systematic review of the literature if applicable
1c. research protocol/grant proposal	Every epidemiologic study, with the aim of publishing the results should be based on a detailed research protocol describing the study. The level of detail is such that another research group is able to carry out the study as intended with the protocol in hand. Once final it is required that the study protocol is ultimately made public, either by placing it on a publicly accessible website or by uploading it in an appropriate studies register
1d. grant submission	Be frank about your project and don't promise more than you can deliver
1e. ethical review	Review by appropriate committee
2a. human volunteers protection	The conduct of the epidemiologic study should be carried out in accordance with the study protocol, and by adhering to the Declaration of Helsinki
2b. data collection	The data collection process is a vital element of any study and therefore should be documented in detail. Include a digital log
2c. statistical analysis	The statistical analysis should be conducted according to the protocol.
2d. report preparation	The report must be an accurate balanced and concise reflection of the conducted study taking into account existing guidelines and it should describe its limitations and deviations from the protocol
3a. manuscript submission	A scientific study is only completed when all its results are properly reported and when the study has been well documented and archived Any protocolled study must be published.
3b. contacts with journalists	the study and its results should be presented to journalists in a reliable and

	balanced manner, without making the results appear to be more (or less) than they really are.
3c. data archiving and sharing	Once the report is in a final form, the study group must ensure that the raw data files and the final dataset used for the statistical analysis are securely stored, protecting privacy of subjects and accompanied by a fully explanatory data description or code book. Data sharing in principle is encouraged and should be the norm, since re-use of data makes research more cost-effective.
3d. document archiving	Throughout the study execution, but also after the study has been finalized, the study group is accountable for its work.

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