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ENCePP Code of Conduct Revision 4

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Code of Conduct – Implementation Guidance for Sharing of Study Data

The purpose of this document is to define clear criteria for sharing data of studies[1] conducted in line with the provisions of the ENCePP Code of Conduct as well as for the procedure for handling requests for access to data by third parties. The guidance follows the principle of maximum transparency whilst respecting the need to guarantee data privacy and to avert the potential for misuse of shared data. It complements the ENCePP Code of Conduct[1] which defines requirements for the conduct of studies to maximise transparency and promote scientific independence throughout the research process.

It is stressed that studies need to comply with relevant legislation, as applicable.

I Background

Researchers and study funders adhering to the Code have committed to comply with a set of transparency requirements including sharing of study data upon request. The Code lays down the following provision requiring researchers to provide access to the study data:

> *(…) Both the study protocol and the research contract should address rules for access to raw data, processed data and results generated under the study. Any personally identifiable data should be maintained under secure conditions in line with data protection legislation.*
>
> *The (primary) lead investigator should ensure that all data collected and generated in the study are recorded in a way that allows verification of the published results whilst respecting data protection legislation. The (primary) lead investigator should provide on request a detailed description of how the raw data were transformed into the data set for analysis and should take all possible steps to provide for audits by competent authorities. The (primary) lead investigator should furthermore be prepared to share upon request the data set used for analysis and all scheduled interim and final study findings - irrespective of results - once the final study report is available and provided data sharing complies with applicable laws and does not infringe the rights of any third party, e.g. license for secondary data. Investigators should respond to requests for access to data in line with the* Implementation Guidance for Sharing Study Data *(see Annex 4).*

[1] Further information on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the ENCePP Code of Conduct can be found at http://www.encepp.eu/.

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Access to data may be requested by a third party for the purpose of corroborating the study results in the interest of public health, and provided the additional research with the shared data is compliant with the Code's provisions for transparency (see Implementation Guidance for Sharing Study Data, *Annex 4 for details). The access request needs to be made on specific grounds and should include a sound justification as well as a protocol on the research to be conducted or the plan for quality control checks, as applicable in order to corroborate the study results. In principle, data should be shared if the grounds based on which access is requested cannot be addressed otherwise (see also Chapter 4.7.2). Access to data should also be provided in response to requests to confirm compliance with the Code or in the context of an audit by a competent authority.*

Investigators should describe the procedure for access to the analytical data set in, or as an Annex to, the study protocol, indicating the degree to which data can be shared and, if access is restricted, including a justification why access is limited. (…)

II Data requirements

It is acknowledged that the degree to which access to study data can be granted depends on the need to comply with data protection legislation (both at European and national level) as well as on the nature and origin of the data. Ideally and in line with the principle of maximum transparency, data are made available as openly as possible.

In any event, the degree to which access is provided should be sufficient to allow addressing the specific issue (see also chapter V) raised by the third party requesting access (hereafter referred to as applicant). To this end, the Code of Conduct requires to provide access to the *analytical data set* and a *detailed description of how raw data were transformed into the data set for analysis*.

II.1 *Analytical data set*

For the purpose of the provision on data sharing as specified in the ENCePP Code of Conduct and this document, the analytical data set is defined as the minimum set of data required to perform the statistical analyses leading to the results reported for the study and which, together with a complete audit trail describing the manipulation of raw data to obtain the analytic dataset, would be sufficient to allow a third party to repeat or corroborate the results. In principle, this can be raw data, provided this is in line with data protection legislation, or an aggregation of the data. For raw data, the complete audit trail should always be available as well. If sufficient to address the issue based on which access to data is requested, it is acceptable to only make available a subset of the full analytical data set.

II.2 *Data privacy restrictions*

To protect the privacy of the study subjects, often it will be necessary to remove personal identifiers from the data set before it can be released to third parties[2]. Studies investigating rare diseases, small geographic areas or involving sensitive information present particular challenges and may require substantial modifications. Such modifications shall not be considered a breach to the Code's requirement to share data. It is also acceptable if access can only be granted on-site and/or involves confidentiality or data sharing agreements.

[2] Practical guidance on preparing raw clinical data before sharing them has been published by Hrynaszkiewicz I, Norton ML, Vickers AJ, Altman DG, Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers, BMJ 2010;340:doi:10.1136/bmj.c181.

II.3 *Detailed description of how raw data were transformed into the data set for analysis*

In order to further increase transparency, the Code requires an audit trail documenting the steps undertaken to transform the data collected in the study (raw data) into the data set used for analysis. This description should be made available alongside the analytical data set if necessary to answer the question for which access to data has been requested.

III Time restrictions

Access to data should be granted whether all data or related results have been published or not. However, access may only be requested after the final study report is available. If possible, sharing of data should not be limited in time. As a minimum, researchers should provide for the possibility to share data up to a period in line with the requirements for the study archive in the Guidelines for Good Pharmacoepidemiology Practices (GPP)[3].

IV Applicant

In principle, any third party may request access to data in line with the provisions of the Code and this document. The applicant requesting access to data should be clearly identifiable (name of individual, affiliation and contact details) and should agree to follow the transparency requirements of the ENCePP Code of Conduct, including provision of declarations of interest (for further detailed see chapter VII).

V Purpose for sharing study data

Requests for access to data must be made on specific grounds either

- with the aim to corroborate the study results in the interest of public health,
- to confirm compliance with the ENCePP Code of Conduct, e.g. to demonstrate that the audit trail established in line with the Code's requirements does allow corroboration of results, or
- in the context of an audit by a competent authority.

Sufficient information needs to be provided to confirm that the request is made for one of the above-mentioned purposes, including a sound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable.

The original researcher may require the conclusion of a data sharing agreement with the applicant restricting the use of the shared data to one of the above-mentioned purposes and/or the protocol. It is at the discretion of the original researchers to grant access to their data in case of requests outside the scope described above, e.g. for use in other research projects such as independent patient meta-analysis.

V.1 *Corroboration of study results*

Access to data with the aim to corroborate published results and interpretations thereof should be provided

- if there is evidence of conflicting results of different/separate studies addressing the same research question. In this case, access to data may be restricted for the sole purpose of identifying differences (e.g. methodological) that explain the discrepancies between the reported outcomes.

[3] According to revision 2 of the GPP (April 2007) the study archive should be kept for a period of five years after final report or first publication of study results, whichever comes later.

- in case of suspected methodological issues which might impact on the study outcome, such as accounting for confounding factors.

V.2 *Audits*

In order for the findings of a study to be used to support regulatory decision making it is essential that the respective competent authority can have access to the underlying data and conduct audits. To this end and as is good practice, researchers should ensure that all data generated in the study are recorded in a way that allows corroboration of the published results. All possible steps to provide for audits by competent authorities should be taken.

VI Replying to requests for data sharing

Researchers should describe the procedure for providing access to data as part of or annexed to the study protocol. If such procedure provides for access criteria, these should be no stricter than those described in this document.

VI.1 *Approaches for replying to data access requests*

Researchers should as far as possible take an open and collaborative approach to data sharing with the aim to corroborate the results of their study. On a case-by-case basis, researchers may choose to reply to access requests in different ways, some of which do not involve sharing of data, including:

1. **Written response:** The original researcher provides a response in writing to the applicant addressing the issue based on which access is requested.
2. **Re-analysis by original researcher:** The original researcher provides the applicant with the outcome of additional data analyses to address the issue raised.
3. **Collaboration:** Both the applicant and the original researcher jointly investigate the issue raised.
4. **On-site access:** Data are shared at the premises of the original researcher only, with or without having concluded a data sharing agreement.
5. **Provision of data:** The study data are submitted to the applicant with or without having concluded a data sharing agreement.
6. **Analysis by an independent third person:** Post-hoc analyses are performed by an independent third person, e.g. statistician or other.

Any of these approaches is in principle acceptable provided that it suffices to address the issue raised by the applicant, and ensures full transparency. In case of studies using secondary data, it may be necessary for the applicant to directly apply for access to the relevant database in line with applicable licence and governance rules (see chapter VI.3 for further details). For audit purposes in line with chapter V.2 on-site access should be granted.

If the applicant has a (perceived) conflict of interest, researchers may decide to reply to the access request in a way that that does not involve actual sharing of data, e.g. using an independent third party to carry out the re-analysis of the data.

If the applicant does not agree with the level of access provided, the matter should be referred to the ENCePP Steering Group for arbitration (see also chapter VIII). Irrespective of the approach chosen to reply to a request, the description of how the raw data were transformed into the data set for analysis (see chapter II.3) should always be made available if requested.

VI.2 *Financial considerations*

Researchers may ask the applicant for compensation of the costs incurred for providing access to and/or additional analysis of data. The amount of the compensation has to be reasonable (preferably based on time actually spent by concerned staff) and not discourage data sharing. The compensation needs to be communicated to the applicant prior to sharing the data.

VI.3 *Licensing and governance rules*

In studies utilising secondary data, i.e. data previously collected for a another purpose and stored in medical charts or electronic records, access to data might be subject to a licence or governance rules which prevent researchers from sharing their data sets with third parties. As a principle, all steps should be taken to ensure the success of a request for data sharing in the most cost-effective way possible, e.g. if feasible, researchers should consider bilateral agreements and provide access to the applicant on-site. Should this not be possible, the applicant can be advised to obtain a licence or to apply for approval at a research committee or to fulfil any other condition required under the governance rules.

VII Compliance of research with shared data with the Code's transparency requirements

There is no guarantee that re-analysing the study data will produce results of a better quality than the original study. The outcome of the re-analysis should always be read in the context of the original results taking into account that it has been done post-hoc.

In order for the applicant to meet the claimed purpose of improving public health, the research conducted with the shared data needs to be equally transparent as the original study. Therefore, any research or review conducted with the shared data should be compliant with the transparency requirements of the ENCePP Code of Conduct:

- Making available the study protocol for the re-analysis of the data including the statistical analysis plan. It is acceptable to include reference to the protocol of the relevant study.
- Compliance with the Code's requirements of declarations of interests.
- Compliance with the Code's requirements as regards the recording and access to data and relevant steps throughout the research process and to take all possible steps to provide for audits by competent authorities.
- Making publicly available the results in line with ENCePP requirements. In particular, the origin of the data should be acknowledged in line with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (ICMJE). In addition to the requirements of the Code the original researcher should be consulted before the publication of the results in order to enable him/her to provide comments.
- Registration in a publicly available register: Notwithstanding the general need to comply with the Code, the requirement for registration of the study in a publicly available register shall only apply if the additional research qualifies as a stand-alone study. In any event, information on post-hoc research with shared study data including the study report and publications of the results should be linked to the original study in the EU PAS Register® (see also Chapter 4.1 and 4.6 of the ENCePP Code of Conduct). To this end, it is the responsibility of the applicant for access to data to provide all relevant material to the original researchers or the ENCePP Secretariat who should add this information to the EU PAS Register®.

VIII Role of the ENCePP Steering Group & arbitration

Whenever there is disagreement between the applicant for access to data and the original researcher the matter should be referred to the ENCePP Steering Group who will act as an arbiter.

Upon receipt of a data sharing request, researchers should respond to the request in line with this Guidance or consult the Steering Group about an appropriate response. If the applicant agrees with the chosen approach, the request should be tabled at the next Steering Group meeting for information only. If the applicant and the original researcher cannot agree on a suitable approach, the ENCePP Steering Group will validate the request against the access criteria as specified in this guidance and decide about an appropriate approach to reply to the request. If the level of detail of the request is not sufficient, further information may be requested from the applicant as appropriate.

Once the Steering Group has decided on a data access request, the ENCePP Secretariat shall inform the researcher and the applicant accordingly. The decision of the Steering Group is binding for the researcher of an ENCePP Seal study and non-compliance will be considered a breach with the ENCePP Code of Conduct.

If, for any reason, access to data is refused, the communication of the related data access request including an explanation for its refusal should be made publicly available on the EU PAS Register unless the applicant withdraws his/her request.

IX References

ENCePP Code of Conduct, (Revision 4: March 2018), available at http://www.encepp.eu/code_of_conduct/index.html.

Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, (Revision 2: April 2007), available at https://www.pharmacoepi.org/resources/guidelines_08027.cfm.

Hrynaszkiewicz I, Norton ML, Vickers AJ, Altman DG, **Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers**, BMJ 2010;340:doi:10.1136/bmj.c181.

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