ISPOR VISION: ISPOR is the leading global scientific and educational organization for health economics and outcomes research and their use in decision making to improve health.

ISPOR MISSION: to promote health economics and outcomes research excellence to improve decision making for health globally.

ABSTRACT

As the leading health economics and outcomes research (HEOR) professional society, ISPOR has a responsibility to establish a uniform, harmonized international code for ethical conduct. ISPOR has updated its 2008 Code of Ethics to reflect the current research environment. This code addresses what is acceptable and unacceptable in research, from inception to the dissemination of its results.

There are **nine chapters: 1 – Introduction; 2 – Ethical Principles** (respect, beneficence and justice) with reference to a non-exhaustive compilation of international, regional, and country-specific guidelines and standards; **3 – Scope**; **4 - Research Design Considerations** (primary and secondary data related issues, e.g., participant recruitment, population and research setting, sample size /site selection, incentive/honorarium, administration databases, registration of retrospective observational studies and modelling studies); **5 – Data Considerations** (privacy and data protection, combining, verification and transparency of research data, scientific misconduct, etc.); **6 – Sponsorship and Relationships with Others** (roles of researchers, sponsors, key opinion leaders and advisory board members, research participants and IRB/EC approval and responsibilities); **7 – Patient Centricity and Patient Engagement** (new addition, with explanation and guidance**); 8 - Publication and Dissemination**; and **9 - Conclusion and Limitations**.

In addition, the ISPOR Code of Ethics Task Force developed a **64-point summary** that is woven through the first eight chapters. The summary, in its entirety, follows the report (p.23). **A glossary** follows. Additional material can be found in **10 detailed appendices** that include: other relevant codes of ethics, HEOR data sources, data protection considerations, recruitment, safety and reporting, incentive and disclosure requirements, IRB/EC roles and research participant involvement. These are in a separate attachment and/or can be accessed via this link to: https://www.ispor.org/TaskForces/ISPOR-Code-of-Ethics.asp

PREAMBLE TO CODE OF ETHICS 2017

ISPOR expects its members to adhere to the highest ethical standards because ISPOR's activities and those of its members affect a number of constituencies. These include, but are not limited to:

- **Patients -** who are ultimately going to experience the greatest impact of the research.
- **Health care professionals -** who will be treating or not treating patients with therapies, medications and procedures made available or not made available due to healthcare research.
- **Decision-makers and Payers** - who must decide what is covered so as to optimize 1) the health of patients and 2) resource utilization. This includes:
    - **Government Groups** - who require the results of healthcare research to set policy and prices.
    - **Insurers** - who base health care coverage and/or payment decisions on healthcare research.
    - **Employers** - where healthcare research affects their decisions on providing health benefits.
    - **Administrators and Others**, such as U.S. managed care personnel, - who need results that are both practical and useful.
- Professional **Outcomes Researchers**
- **Pharmaceutical Manufacturers** - whose products are often the subject or focus of healthcare research.
- **Colleagues** - where relationships in conducting research and related activities are particularly critical.
- **Research employees** – who are concerned about how they are regarded, compensated and treated by the researchers for whom they work
- **Students** - where respect and appropriate behavior by researcher / employers is important. They are the future of the profession.
- **Clients** - for whom healthcare research is conducted and researcher relationships are maintained.

Through behaviors and practices intended to ensure that healthcare research is designed, conducted, and reported in the most proper and ethical way possible, the Code is a means for the science of health economics and outcomes research to avoid or address credibility challenges based on methodology or bias concerns. By accomplishing this, the various affected constituencies will be able to trust and benefit from research findings as much as possible. The Code also includes some general ethical considerations for the Society.

As part of membership, members agree to compliance with ISPOR's Code of Ethics when they join or renew. However, we recognize that members' own organizations may also have ethical codes that should be followed. We also recognize legal considerations may sometimes be important, for example, in relation to employment law. ISPOR may deny or revoke membership, participation in groups or meetings if a member is convicted of a felony or other act or moral turpitude, or upon suspension of a license in a medical or health profession.

CHAPTER 1: INTRODUCTION

As the leading health economics and outcomes research (HEOR) professional society*, ISPOR has a responsibility to establish a uniform, harmonized international set of standards or guidelines for members to follow. Since 1998, an ISPOR Code of Ethics (Code) has been publicized to HEOR

* Pharmacoeconomics is a sub-discipline of health economics. The ISPOR Code of Ethics uses the broader term, health economics, combined with outcomes research to form health economics and outcomes research or HEOR, which has become predominant since ISPOR was founded more than 20 years ago.

practitioners. This latest 2107 edition reflects the changing environment in which ISPOR and its membership conduct research.

Those practicing in the HEOR area have a long history of civil discourse and of developing "good practices" associated with different research designs. Such discussions and the templates developed are ways to reduce the unwarranted variation in professional outputs. Nonetheless, a code of ethics differs from a recommended good or best practice recommendation. It is concerned with principles, such as informed consent, data privacy and equity in healthcare.

The core principles embodied in a code of ethics represent values that, on one hand, must not be compromised but, on the other hand, may need to be weighed against one another. They are the guiding standards that are essential for the professionalism of researchers, and the confidence that users and members of other professions can have in HEOR.

The composition of ISPOR as an organization is an important preface to what is to follow. The global nature of ISPOR sets it apart from many other organizations, with differences in cultures and sometimes, points of view on important issues, such as data privacy. ISPOR members represent multiple disciplines that approach intellectual problems in HEOR with a variety of tools and research designs. They differ in the relationships that they have with different healthcare systems around the globe. They come from diverse employment settings with complex and dynamic structures.

As a multidisciplinary, global organization, ISPOR strives for representativeness, transparency, and balance in its activities, thereby, avoiding the appearance of bias or conflict of interest. This includes, but is not limited to, sponsorship of its conferences and other activities, as well as presenters at its conferences. To the extent that it is feasible, ISPOR program planning and selection committees should have a membership representative from all of its major constituencies. ISPOR should also have a Board of Directors that is representative of the various constituencies the Society serves.

Furthermore, because significant research funding will come from funders with interests in specific findings (at times commercial, private non-profit, as well as governmental institutions, all have hoped-for outcomes), ISPOR should continue to maintain its own statement of objectivity and autonomy. ISPOR strives to assure that its journal, Value in Health, only publishes papers that have gone through a rigorous peer-review process, and whose authors are listed pursuant to strict criteria.

Even though economics is a major part of ISPOR's identity, price and coverage discussions, and similar topics, should not be construed as encompassing ISPOR's total identity. Rather, ISPOR is conscious of broader ethical issues impacting global and regional medical resource allocation, public health policies and the global healthcare environment, and, on the research side, topics such as patient autonomy, patient outcomes and research conduct. These issues include, but are not limited to: prejudice, equity in healthcare delivery, and access.

The HEOR profession and research landscape have changed dramatically since the publication of the current Code in 2008[1] (Appendix 1) with the increased collection and use of real world data, rise of health information technology (IT), genomic information, focus on patient centricity, social media, and privacy issues, among others. Furthermore, most professional codes that ISPOR referenced in the past have been updated since last publication. Finally, due to the Society's immense growth in both membership and geographic coverage, it is important to recognize that there may be conflicting standards of professional conduct in regions of the world that now need to be considered in ISPOR's Code (version 4).

Rather than merely reducing unwarranted variance, a code of ethics is intended to promulgate the standards that define what is acceptable and unacceptable in the conduct of all aspects of research, from its inception to the dissemination of its results. This revised Code represents a collective effort to articulate those standards.

Therefore:

- ISPOR should publicize this Code of Ethics to members and non-members involved in pharmacoeconomics and outcomes research.

- ISPOR should strive for a balance in sponsorship of its conferences and other activities by providing criteria for accepting of funding and ensuring full transparency, thereby avoiding the appearance of bias or conflict of interest.

- Because, as a practical matter, most funding will come from different entities, ISPOR should continue to maintain its own statement of objectivity and autonomy.

- ISPOR should strive to assure that its journal, Value in Health, only publishes papers that have gone through a rigorous peer-review process.

- ISPOR should have a Board of Directors that is representative of the various constituencies the Society serves.

- The ISPOR program planning and selection committees should have membership representative of all of its major constituencies.

- Like other professional societies, ISPOR should be conscious of broader ethical issues impacting global and regional medical resource allocation, public health policies and the global healthcare environment, and research topics such as patient autonomy and research conduct. These issues include, but are not limited to: prejudice, equity in healthcare delivery, and access.

CHAPTER 2: APPLICATION OF ETHICAL PRINCIPLES TO THE ISPOR CODE

Both the past and the current Code of Ethics draw from international standards and guidelines. A non-exhaustive compilation of international, regional, and country-specific guidelines and standards in the research field including patient engagement resources and publication ethics codes was reviewed and summarized (Appendix 2). This range of standards includes, but is not limited to, the Belmont Report, the International Conference on Harmonization Good Clinical Practice (ICH GCP), the Agency for Healthcare Research and Quality (AHRQ) of the United States, the European Federation of Pharmaceutical Industries and Associations (EFPIA), Guidelines for Research Ethics in Japan, and the Genetic Alliance for patient engagement.

Therefore:

- Members should maintain a current knowledge of research practices, with due consideration of those practices most relevant to the research that is being done in their own countries.

The ISPOR Code closely follows the Belmont Report's three fundamental ethical principles that form the basis for the National Commission's topic-specific reports and the regulations that incorporate its recommendations. Application of these principles requires careful consideration of informed and

voluntary consent, risks and benefits, and the selection of participants for research.

Respect for persons: protecting the autonomy of all people; treating them with courtesy and respect; and allowing for informed and voluntary consent. Researchers must be truthful and conduct no deception;

Beneficence: the philosophy of "Do no harm" while maximizing benefits for the research project and minimizing risks to the research participants; and

Justice: ensuring reasonable, non-exploitative, and well-considered procedures are administered fairly — the fair distribution of costs and benefits to potential research participants — and equally.

ISPOR's Code places additional emphasis on privacy, transparency and civility. This reflects the responsibilities associated with increased data access, the global nature of research, and a broad range of research participants and health care system stakeholders.

Therefore:

- Privacy: Members who work in HEOR can be privy to data sources containing protected health information (PHI) and other personal data from patients. It is essential that these data are handled with utmost care so that patient confidentiality be maintained at all times and no breaches to patient privacy occur.

- Transparency and Integrity: Members must disclose research methods in sufficient detail to permit replication. The funding sources should be clearly acknowledged, and any conflicts of interests declared. Designing, conducting and especially reporting of the study should be an unbiased reflection of the full range of findings generated.

- Civility: Members' research and discussion should respect the dignity of all participants. Respecting the dignity of patients and providers of care is clearly a responsibility. It is also a responsibility to treat fellow researchers with respect.

All HEOR studies should respect and protect the human subjects enrolled in those studies, using the principles of the Declaration of Helsinki (1964-2013).[2] Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research participants.

CHAPTER 3: SCOPE OF THE CODE

The ISPOR Code of Ethics is specifically oriented to HEOR. While there is overlap with other fields, our goal is a discipline-oriented Code. It is important to note that the scope of this Code of Ethics does not include ethical considerations related to the use or impact of specific HEOR measures, e.g., potential age-related biases implicit in quality-adjusted life years.

ISPOR's Code of Ethics covers the conduct of HEOR, but not societal decision making based on HEOR evidence, such as formation of HTA policies. As long as reporting of research is complete and

transparent, users of ISPOR members' research can judge use or impact issues independently. For more on these issues, please refer to the Second Panel on Cost Effectiveness in Health and Medicine.[3]

Health economics is a branch of economics, a discipline that analyzes the economic aspects of all activities designed to improve or maintain health and health care, typically focusing on the costs (inputs) and the consequences (outcomes) of health care interventions. It is concerned with issues related to efficiency, effectiveness, utility, value, quality, ethics and behavior in the production and consumption of health and health care. In broad terms, health economists study the functionality of health care systems and health-affecting behaviors.[4]

Outcomes research is the scientific discipline that evaluates the effect of health care interventions on patient well-being, including clinical, economic and patient-centered outcomes. (ISPOR Book of Terms)

Difference and relationship to other research fields

HEOR is closely related to other common research types, such as clinical trial/studies, non-interventional observations, epidemiologic investigations, real world research and market research studies (See Appendix 3 for more information).

There is no single legal instrument or practical guidance for HEOR. At times, this results in differences in definitions and terms across groups and countries. HEOR can utilize any techniques from the research types mentioned above. The objective is to evaluate the effect of health care interventions on patient well-being, including clinical, economic, and patient-centered, and other relevant outcomes, as well as the functioning of health care systems and health-affecting behaviors.

Therefore:

- Members should adhere to the standards of practice for their respective fields of research and identify any official guidelines and standards used.

This 2017 Code of Ethics covers the following five topics in depth: research design, data considerations, sponsorship, patient engagement, and publication and dissemination with appendices providing ancillary detail to these sections.

CHAPTER 4: RESEARCH DESIGN CONSIDERATIONS

HEOR comprises a range of research designs from modeling and retrospective analyses using secondary data to prospective observational and clinical trial designs (See Appendix 4 for more on HEOR data sources). No matter the chosen research design, HEOR is conducted following the core scientific principles of objectivity, transparency, reporting, and quality assurance. It is defined by the objective(s) and the approach, not by the title of the work or the role of those commissioning the work.

Primary Data-Related Research Considerations

Participant Recruitment

ISPOR recognizes that study participants can be recruited via a number of methods.

Therefore,

From the point of "first contact" researchers should provide potential subjects information about study intentions and how the research is funded, as well as all information mandated in their proposals as reviewed by institutional review boards (IRBs)/research ethics committees (RECs). (See Appendix 5 for more details.)

Population and Research Setting

Researchers should be specific with regard to population and setting.

Therefore,

Members should describe the analytic study population in terms of persons, geography, time period, and selection criteria. Members should choose, and obtain permissions to use, a suitable research setting and/or existing data or literature to provide information about a specific population to which the study results are meant to apply.

Sample Size, Site Selection

Study sample size should not be larger than statistically necessarily. Inadequate sample size (too low) may provide insufficient data to answer the intended research questions or will provide low precision[5].

Therefore,

The number of patients and sites selected for a study should be appropriate to meet the research objectives.

Safety / (Serious) Adverse Events

Safety and adverse event reporting (AER) is an important aspect of all primary research involving patients and medical interventions. The Guideline on good pharmacovigilance practices (GVP)[6] laid down in the European Union's Directive 2010/84/EU[7] applies to investigational medicinal products and non-investigational medicinal products. Similar regulations exist in most other jurisdictions. AER is applicable to some HEOR activities, including clinical trials, primary research, non-interventional studies, market research, and real world research. (For more information, see Appendix 6.)

Researchers are expected to collect and report adverse events, not only due to regulatory and legal requirements, but also with an understanding of the responsibility to patients and society to comprehensively inform the safety of treatment options.

A strong international collaborative approach to post-approval surveillance and mandatory adverse reporting is critical. Data collected through social and digital media can be useful, but often do not follow clear pharmacovigilance reporting guidelines because there is no single marketing authorization holder.

Therefore:

- The balance of risk or harm to benefit for patients must be considered in HEOR studies, and must be communicated to patients via informed consent.
-Safety and adverse event reporting (AER) are important aspects of all primary research involving patients and medical interventions, are applicable to many HEOR activities, and must follow international guidelines.

Incentive/Honorarium

An 'incentive' or honorarium is any benefit given to a participant to encourage participation in a research study. It is commonly used in prospective research and surveys to provide participants with compensation for expenses that may be incurred as part of participating in research. Remuneration is compensation to investigators or consultants for their work or contribution to the study. For specific details on incentives and honoraria, see Appendix 7.

Therefore,

Any such proposed payments are, of course, subject to receivers and providers' internal compliance guideline and IRB/EC approval, and must be detailed in the research proposal submitted for review.

Researchers need to be diligent in ensuring that the incentive would not induce research participants to accept risks they would not be willing to accept if they were offered a smaller or no incentive.

Secondary Data-Related Research Considerations:

Administrative Databases and Other Large Datasets

Health care systems generate operational and administrative data that have been used extensively in HEOR studies. HEOR uses a wide range of secondary research sources, including proprietary databases, claims databases, patient registries, routine data sources, systematic reviews, evidence synthesis, social media, Internet of Things (IoT), and other related sources. Data can range from a longitudinal administrative database to a constant flow from IoT and wearable devices, or from controlled clinical trials to unstructured social media feeds.

Examples include governmental databases like the US's Center for Medicare and Medicaid Services (CMS), Chronic Condition Data Warehouse (CCW), SEER Medicare[8], the United Kingdom's HES[9], France's SNIIRAM[10] etc., as well as a number of private databases. Some research involves combining various datasets (e.g. Medicare Current Beneficiary Survey and Medicare Claims Parts A, B, C or D). This diversity in types of datasets presents multiple analytic challenges.

Because the data were initially collected for another purpose, the key first step for those creating and then using secondary data is to be sure that all intellectual property rights have been respected and that the appropriate permissions have been secured. This is typically done by the database supplier. These permissions include protection of the privacy of the individuals whose characteristics are captured in the database, as well as their informed consent for secondary use of their data, where applicable. Privacy is discussed below.

The cost of creating databases for secondary use is sometimes borne by governments and the users are charged nominal fees. When private entities build databases for secondary use they will often do so in anticipation of higher user fees that make database creation and distribution a worthwhile commercial endeavor. In either case, the researcher needs to be assured that the database was legally and ethically constructed.

The vast majority of HEOR studies currently conducted involve the analysis of secondary data. Retrospective observational studies are often conducted using administrative databases or clinical registries. Modeling studies involve the synthesis and analysis of data from several sources, including previously conducted clinical trials, clinical registries, routinely available cost data, and the published

literature. The use of secondary data has ethical challenges related to the collection and storage of personal data that are different from those in primary research studies (discussed above), since the data are already anonymized. If there is doubt or moral concern regarding how the secondary data were generated, researchers can consider a due diligence process on the data source before using it, or can use an alternative dataset for the study.

There are instances where a secondary database may not be considered de-identified. One example is the CMS Chronic Condition Warehouse where age and postal zip code information are included. However, given the large degree of analyst discretion, secondary research studies do raise a number of ethical challenges relating to the avoidance of methodological bias due to the selective use of the available data and the inappropriate use of assumptions regarding such things as missing data, the nature of selection bias, outliers, and so on. Therefore, the most important general ethical principles in the analysis of secondary data are those of 'transparency and reasonableness, i.e., in the absence of consensus on principles, a fair process allows us to agree on what is legitimate and fair.'[11]

Therefore,

- *When using secondary data sources initially collected for another purpose, HEOR researchers should ensure that intellectual property rights are respected and that all the appropriate permissions have been secured.*

- *Given the potential for bias in the analysis of secondary data, the most important general ethical principles are those of 'reasonableness' and 'transparency'.*

Registration of Retrospective Observational Studies

For purposes of this Code, observational studies are defined as analysis of existing datasets.[1213] While the registration of research is more common for clinical trials than for observational studies, Williams et al (2010) argue that 'Much of the rationale for the prospective registration of clinical trials applies to the registration of observational studies'.[14] These obligations include oversight by ethical review boards, informed consent, and public release of the study findings to advance biomedical knowledge. As with clinical trials, incomplete reporting of observational studies has been documented. Some researchers suggest that observational studies are also at increased risk for publication bias or other types of bias, including misrepresentation of pre-specified analyses or disease classification coding. Such biases are a concern because they undermine the validity of observational studies, which are an important component of the medical evidence base in areas of public health, such as detection of rare adverse events.

Therefore,

- In those instances in which study methods include analysis of a database, members should describe approaches, methods, technologies used to ensure data completeness and validity as well as the software package(s) used for data analysis. Members should have the education, training and experience to perform the assigned tasks.

- While registration of observational studies is generally not required at this time, members are encouraged to register such studies prospectively to recognize ethical obligations to patients and to avoid the potential for publication bias.

- Where a HEOR study is being conducted alongside a clinical study gathering data prospectively (such as a clinical trial or observational study), where possible members should ensure that the clinical study concerned has been registered on ClinicalTrials.gov, Patient Registries (e.g. patientregistry.ahrq.gov), EU electronic Register of Post-Authorisation Studies (EU PAS Register)[15], or equivalent database in their own country.

ISPOR has published a number of Good Practices for Outcomes Research Reports[16] on conducting outcomes research (clinical, economic or patient-reported) or using outcomes research in health care decisions. While these reports do not address ethical principles directly, the specification of good research methods is an important component of recognizing and eliminating analytic bias.

Modeling Studies

In these HEOR studies, secondary data from multiple sources are synthesized using a decision-analytic model. Although this is the main application of modeling, models are sometimes used to extrapolate costs and benefits beyond the end of a clinical trial in a primary research study. The ethical principles discussed here apply equally to both situations.

The general ethical principles of reasonableness and transparency suggest a number of approaches for the conduct of modeling studies. ISPOR with the Society for Medical Decision Making published seven Modeling Good Research Practices Task Force Reports[17]. The seventh, on model transparency and validation[18], is the most relevant task force report to the ISPOR Code of Ethics.

Therefore,

In conducting modeling studies, members should ensure that the input parameters are estimated based on a comprehensive review of the available literature. For the key parameters of the model (e.g., the estimate of relative treatment effect) it may be necessary to conduct a full systematic review and meta-analysis.

However, decision-analytic models typically rely on numerous parameter estimates and it will not be possible to undertake a full systematic review for each. Therefore, members should be transparent about the estimates they use for key parameters, provide the logic they used in selecting particular estimates and explore the impact of their choices through sensitivity analysis. (Sensitivity analysis is widely used in economic evaluation and explores the sensitivity of the study results to the variation in the input parameters.)

Another important feature of modeling studies is the need to make assumptions, either about the parameter estimates in situations where data are absent or inadequate parameter uncertainty[19], or about model structure (structural uncertainty). The ethical principles of reasonableness and transparency would dictate that any assumptions are clearly explained and justified. In addition, sensitivity analyses should be conducted to explore the importance (in terms of the overall estimate of cost-effectiveness) of the assumptions made.

Reporting is discussed further in Chapter 8: Publication and Dissemination.

CHAPTER 5: DATA CONSIDERATIONS

This section provides guidance on data considerations in privacy, data protection, combining research data, data validity[20], transparency, and scientific misconduct. Members should ensure selection of suitable data sources and adequate sample size to power the question(s) being studied.

Privacy and Data Protection

Protecting participants' privacy is paramount to all forms of clinical research, including HEOR. Regulations such as the EU GDPR[21] U.S. HIPAA[22]), Japan APPI[23] cover the collection of data relating to an identifiable person. For data protection purposes, original holders of personal data can, if contractually bound, transfer personal data to other parties without seeking additional explicit permission of the data subject, as long as the data are being used for a purpose for which the original holder has a lawful basis to process the personal data, including the consent of the data subject. This would need to be an integral part of the informed consent process and would require IRB approval. Details of data processing, security, storing, transfer, and participants' rights to their personal data are detailed in Appendix 8.

Combining Research Data

It is sometimes possible to enrich an existing database by linking additional information that is relevant to the individual patient or the provider. Examples include linking socioeconomic information about the neighborhood surrounding the patient's home or the training history of the specific provider delivering a service. The most effective linkages take full advantage of the identifying characteristics of the patient or the provider. Adding data to an existing database can lead to the subtle erosion of privacy protections. As a result, some database providers insist on limiting potential links. It is critical to protect the commitment to privacy during and after the linkage of additional data. Combining of research data must also have been approved by the IRB.

Data Verification

On occasion, access to these data may be requested by journal reviewers or other researchers wishing to verify the analyses used in the research. It is important that researchers, sponsors and the owners of data recognize that the credibility of the research is lessened if other parties cannot adequately verify it.

This is particularly important if one of the objectives of the research is to inform health care decision makers, who in turn may have to justify the basis on which they made a particular decision. This suggests that the maximum level of access, within the law, should be granted by researchers to anonymized, group-level data and that the contracts for undertaking the research should reflect this consideration.

Therefore:

- When a database (from primary data collection and/or secondary data use) is analyzed, members should provide a description of approaches, tools, and technologies used to store the data and maintain patient privacy/confidentiality and de-identification.

- Personal data should be maintained securely and adequate back-up should be maintained. Data access should be limited to authorized individuals. Control systems should be put in place to ensure authenticity, integrity, and confidentiality of data records when transmitted electronically.

- Researchers should offer the maximum level of access to the anonymized, group-level data used in

their research. If data access is restricted by proprietary or contractual considerations, those considerations should be disclosed. If journal reviewers deem it important that statistical review of proprietary data be conducted, authors should work with both the data owners and the reviewers to find appropriate confidential arrangements for such review whenever feasible.

Transparency of Research and Data

Transparency and replicability are crucial to HEOR. Transparency of data and replicability of results are important issues that pose challenges for authors, reviewers and journals (Cochrane 2015)[24]. Some journals have explicit data policies; ISPOR's journal *Value in Health* has its own, and ISPOR members – as well as all contributors – are expected to comply with this policy[25].

Nevertheless, it is recognized that for many, if not most reviewers, detailed review of data, programs, and results is not feasible in the context of performing a timely manuscript review. For those who are able to do so, such review is encouraged (see Cochrane 2015). Those who are not able to do so, but have reason to believe that data review is indicated, should inquire with the editor about the possibility of employing an independent statistical reviewer.

Therefore:

- Members' hypotheses and research designs should be defined a priori, reported transparently, defended relative to alternatives, and planned to recognize and minimize all types of bias.

- Members should fully disclose the identity of sponsors of their research.

- Members should strive to avoid bias and the appearance of bias in conducting research, such as in the choice of methods and data inputs, or in the selective reporting of results

- Members should be aware of conflicts of interest and the appearance of conflicts of interest. As a point of reference, members should look to the rules on disclosure of potential conflicts of interest laid down by major peer-reviewed journals and their own institutions.

- Members should maintain their professional autonomy and objectivity in conducting and reporting, in writing or verbally, research findings.

- Methods sections of papers should identify and justify all departures from the a priori analysis plan.

For authors, posting of data and programs is good practice and strongly encouraged whenever feasible. Best efforts should be made to make them at least available to reviewers when requested, under confidential arrangements, if necessary. When citing articles in a manuscript, known replicability of those articles' results should be an important consideration. This is particularly true for those that are influential to the manuscript's approach or conclusions.

Similarly, transparency of data and replicability of research results should be serious considerations for those organizing conferences, discussing papers, serving on awards or selection committees, writing promotion or tenure letters, hiring researchers, etc.

Scientific Misconduct

Scientific misconduct is the violation of standard codes of scholarly conduct and ethical behavior in

professional scientific research. According to the ICMJE[26], it includes, but is not necessarily limited to: data fabrication, data falsification including deceptive manipulation of images, and plagiarism. See also Chapter 8: Publication and Dissemination.

The Committee on Publication Ethics (COPE) has developed procedures for editors to follow if there are concerns about the integrity or conduct of work in submitted or published papers or if scientific misconduct is suspected. The procedure emphasizes transparency and accountability throughout the investigation, as well as communication of the whole process. While some may consider failure to publish clinical trial results or other human studies a form of scientific misconduct, each situation of alleged misconduct requires individual assessment by relevant stakeholders.

Therefore:

- Members should maintain and protect the integrity of data used in their studies as well as on any other aspect of their research, as previously discussed (e.g., respect for patient autonomy such as informed consent and data privacy).

- Members should not draw conclusions beyond or inconsistent with what their data would support and discuss any limitations in a transparent manner.

CHAPTER 6: SPONSORSHIP AND RELATIONSHIPS WITH OTHERS

HEOR sponsors range from life sciences industry and health care insurers to provider and patient associations and governmental bodies. However, it is understood that much of the funding available to those who pursue HEOR is provided by bodies with vested interests. A central principle of ISPOR's work is the maintenance of its own objectivity and autonomy from sponsors and commercial interests.

Researchers

Those who conduct HEOR should strive to make the nature, scope, and potential of their work clear to sponsors. This not only includes being transparent about the kind of knowledge scientific research can generate but also pertains to the ethical dimension of conducting research. Thus researchers should make it clear to sponsors that all outputs from a research project will include the acknowledgement of all sources of funding as part of a conflict of interest declaration.

Furthermore, researchers should not only avoid being placed in a position where they experience a conflict of interest, they should also avoid the appearance of a conflict of interest, and the possibility that their research will be perceived as biased.

When engaging with sponsors, researchers should be clear about the need to maintain their professional autonomy over all stages of the research, including its design, conduct, and publication. The autonomy of science contributes to the objectivity of research and, therefore, the authority of the researcher.

Sponsors should be informed about the opportunities to enter studies into research registries, as well as their rights (or lack thereof) of access to - and ownership of - the data generated or collected as part of the research.

When researchers accept sponsorship for a particular project they should be in a position to conduct the research in a manner that is both timely and reflects the required level of scientific quality and methodological rigor.

HEOR is conducted through close collaboration within teams and between teams, nationally and internationally. The principle of civility is important to ensure that the contribution from all parties is respected and understood. Employees and employers have responsibilities to ensure that reputations, rights, interests of all parties are respected, and that work is done to appropriate standards protecting proprietary information. Particular care should be taken to ensure that there is no perception of actual abuse of the relationship between more senior faculty members and students.

Therefore:

- Members should respect the reputations and rights of colleagues when engaged in collaborative projects.

- Members should treat their research employees with respect and should compensate them fairly for their work.

- Members should protect and promote the interests of their employers, provide competent work, adhering to these broader guidelines, and protect proprietary information.

- Members should treat students with respect and refrain from exploiting them under any circumstances.

Responsibility to Sponsors

HEOR must not be used to obtain confidential information about competing products and companies from participants who are bound by confidentiality agreements with those companies.

A researcher may transfer any or all of the researcher's research duties and functions to one or more subcontractors (e.g., CROs). All parties, including subcontractors, should be contractually bound by the same legal and ethical requirements as the main researcher.

Therefore:

- Members acting as sponsors should allow HEOR researchers at all times to maintain their scientific integrity and adhere to relevant standards in conducting and reporting research.

- Members should respect contractual rights when they agree to perform work for hire and should refrain from disseminating information which they agreed in advance to keep proprietary.

Key Opinion Leaders (KOLs) and Advisory Board Members

The role of KOL brings some ISPOR members into close contact with sponsors. As such, we reiterate the centrality of independence, professional autonomy and objectivity to the scientific process, including dissemination of scientific findings.

Therefore:

- When acting as KOLs, ISPOR members should be transparent about payments – and any other benefits - they receive for acting in this capacity.

- When acting as KOLs, ISPOR members should ensure that the information they are presenting is an accurate representation of the facts available. They should respond to questions and queries honestly and to the best of their abilities.

- When relying on KOLs, ISPOR members should critically engage with the claims being made. Where appropriate they should seek independent corroboration of any factual claims and consider the full range of alternatives for themselves.

- When acting as Advisory Board Members, ISPOR members should maintain their independence and professional autonomy and act transparently, e.g., declare conflicts of interest.

Responsibility to Research Participants

Researchers should be open and transparent about the aim and objectives of their research, its design, its conduct and its potential consequences or outcomes. They should be clear with participants about what is being asked of them, the right to refuse to participate, and the possibilities of withdrawing at a later date.

While it might not always be possible, realistic or particularly desirable, researchers should, where appropriate, aim to communicate results of research to participants. Responsibilities to communicate aggregated results to participants should be clearly stated in consent materials or processes.

Informed consent is the tool to ensure that trial participants understand the context and specifics of clinical trials and/or health care-related research. The informed consent document should be relevant, easily understandable and practical. It should not serve as a theoretical exercise for the researcher. A copy of the signed informed consent must be provided to the participant.

Ethical review of research proposals should, where appropriate, seek input from individuals or organizations that are able to represent the perspective of patients.

Therefore:

- Members should respect the autonomy of research participants in designing and conducting studies, specifically, but not limited to, informed consent and data privacy.

IRB/EC Approval

Sponsors should ensure that IRB/EC approval is obtained, as appropriate for the planned research. It is the responsibility of an IRB/EC to ensure that the rights, safety and well-being of those involved in research are protected. Furthermore, it should provide public assurance of that protection by, among other things, reviewing and approving / providing a favorable opinion on the research proposal, the suitability of the investigator, facilities, and the methods and material to be used in obtaining and documenting informed consent of research subjects.

Requirements of the IRB/EC approval shall depend on the research type, study objectives, interaction with patients and competent authority requirement from different countries. Some recommendations of

IRB/EC for different studies appear in Appendix 9. The legal status, composition, function, operations and regulatory requirements pertaining to independent ethics committees may differ among countries.

Appendix 10 provides for involvement of different participants groups, including healthy volunteers, patients, protected classes, children and vulnerable populations.

CHAPTER 7: PATIENT CENTRICITY AND PATIENT ENGAGEMENT IN RESEARCH

The ISPOR Code has been updated to appropriately reflect an increased focus on patient centricity and patient engagement in research by regulatory and health technology assessment (HTA) agencies, policy and decision makers, medical technology manufacturers, research organizations, payers and other stakeholders seeking to understand patients' perspectives and experiences. Organizations support patient centricity in research for a number of reasons from improved research, utility and efficiency of clinical trials to ethical concerns and societal and moral obligations. Furthermore, the involvement of patients or their representatives increases transparency, mutual respect and trust between patients and other stakeholders, including payers and providers.

Reflecting this evolution in the research environment, as an organization, ISPOR has moved to become more patient-centered. It aligns with ISPOR's members' interests and ISPOR's overall mission to promote health economics and outcomes research excellence to improve decision making for health globally. In 2015, the ISPOR Board of Directors unanimously approved a motion to create a special category of membership within ISPOR for patient representatives to increase patient involvement throughout ISPOR's activities.

Understanding Patient Centricity and Patient Engagement

As of 2017, there is no standard definition of patient centricity or patient engagement. Significant variation exists in how different stakeholders and sectors (e.g., regulators, HTA agencies, the pharmaceutical industry, academia, hospitals, and patient organizations) define these terms.

Patient-centric research should focus on the outcomes that are meaningful and important to patients, with "those outcomes important to patients' survival, function, or feelings as identified or affirmed by the patients themselves, or judged to be in patients' best interests by providers and caregivers when patients cannot report for themselves."[27] In order to understand what is important to patients, they must be meaningfully engaged in the research from start to finish. Patient-centered outcomes may or may not be measured by patient self-report[28].

Operationalizing Patient Centricity and Patient Engagement

Levels of Patient Engagement

Patient engagement can take many forms. Examples of little or minimal engagement include asking for patient input by gathering patient reactions and regarding patients as study subjects only. It is low intensity engagement with unidirectional communication.

More meaningful levels of engagement include collaboration and bi-directional communication. Examples include patient experts in an advisory role providing *a priori* consultation on study design, procedures and\or outcomes. It is more active, higher-intensity involvement between researcher and consumer or patient representatives. At the high end of the engagement spectrum is shared leadership and partnership, characterized by *a priori,* as well as continuous interaction. At this level, patients have

a governance role and are paid investigators or consultants. At the highest level of engagement, the research is patient-driven.

There are a number of useful frameworks for patient engagement[29]. They describe (1) patient involvement through interchange between the patient and provider; (2) the stages of research in which patients can be involved; and (3) prioritizing stakeholder engagement in research. They serve as a conceptual basis for patient engagement in medical product development.

Researchers should also consider the role of families and family caregivers when taking a patient-centered approach. Some patients will be unable to engage due to their age or condition. For some illnesses, there is a significant impact on family life and family caregivers. It is important to include family and caregiver engagement under these circumstances.

Timing of Patient Engagement

Patient input is valuable throughout the medical technology's lifecycle from early development through dissemination and post-market surveillance. Early and meaningful involvement of knowledgeable patient representatives and members of patient organizations in setting research questions is highly recommended. Collaboration with patient organizations as part of the research team is also encouraged. To accurately capture patients' values and preferences, patients should be involved in benefit/risk evaluation and related activities throughout the development lifecycle. A planned sequential approach is recommended where feedback from patients is collected and considered[30].

The patient perspective is especially critical in early phases to determine unmet needs and the correct study endpoint(s) for medical label claims.[31] Patient input at the study design stage can improve site selection and recruitment, (e.g. within indigenous or other historically disadvantaged populations), data collection, and reduce patient burden. Patients (or patient organizations), should actively contribute to trial documents directed at patients to ensure that the content and format are understood.

Patients and patient organizations can also help in the translation of research results by helping to develop and share lay-person-level summaries of clinical trial results. Finally, patient input is also needed in assessing real-world effectiveness, cost effectiveness, and value. These assessments should be enriched with patient input and guided by patient experiences[32].

Partnering with Patient Organizations

Collaboration with patient advocacy organizations can be a sound platform for successful patient engagement. Researchers will need to familiarize themselves with the many types of organizations that vary in size and scope (e.g. rare versus high-prevalence diseases; local, regional to international). They have a range of experiences, organizational cultures, governance structures priorities, and ability and capacity to engage.

Ethical Considerations

Ethical issues often arise in the patient engagement process[33]. Thus, following established protocols and guidelines is recommended. Rare Diseases Europe (EURORDIS) has published a Charter for Collaboration between Sponsors and Patient Organizations for Clinical Trials in Rare Diseases[34]. The European Patients' Academy (EUPATI) has developed guidance for stakeholders as well[35].

A research contract between patients and research partners is also recommended, even if patients are driving the research themselves. The contract should be respectful and clearly outline roles and deliverables. The contract should recognize patients as experts in their health condition and compensate

them appropriately. Further information on written agreements and compensation are available from EUPATI[36], PCORI[37] and the European Federation of Pharmaceutical Industries and Associations (EFPIA)[38].

Researchers should recognize that patients are not trained researchers. Researchers should recognize patients' input in framing research questions and selecting correct methods for study conduct versus driving the research methodological or analytical approach. However, patients' opinions should be included throughout in the research lifecycle.

Therefore,

- Stakeholder input, including patients (and representatives of patients such as family caregivers and advocacy organizations) in study development, can strengthen the study design and utility:

- Patient input is valuable throughout the research lifecycle from early development to dissemination and post-marketing surveillance.

- Researchers should involve patients and their representatives as partners before, during, and after conducting research.

- To prevent or address ethical issues arising in the patient engagement process, following established protocols and guidelines is recommended.

CHAPTER 8: PUBLICATION AND DISSEMINATION

The main purpose of publishing, or otherwise disseminating HEOR, is to provide reliable and relevant information related to health care treatments and programs. Therefore, it is important that members submitting manuscripts ensure that these contain no inaccuracies, nor misrepresent the data. Publications can discuss methodological principles, the results of empirical studies, or policy choices. The main users of HEOR include decision makers concerned with population-based choices, health professionals deciding on treatment options, and patients wishing to understand more about the treatments available.

Scientific Misconduct: Plagiarism

Plagiarism - the act of passing off as one's own any writing, verbatim or paraphrased, that which was authored by another - is perhaps the most fundamental ethics violation for any author in any field of endeavor. Copyright laws protect writers' words as their legal property. Furthermore, it is extremely important to give comprehensive citations in order to avoid unintentional plagiarism.

In the health and medical sciences, including HEOR, there is a gray area as to what constitutes plagiarism in the context of an individual author publishing new work that is similar in many respects to prior work on which he or she was one of several authors. On occasion, an author is invited to submit a special article or book chapter due to prior participation in an area of important research with the expectation that their contribution will derive from the prior work. In these instances, it is important that the author double-check to make sure that no written material (or tables or figures) is being replicated from the earlier work without permission from the copyright holder.

In addition, ISPOR initiated a scientific and health policy group publication rule that "*No member of an ISPOR Task Force or Special Interest Group should publish any material from an upcoming report, public presentation, or project deliverable without first consulting the larger group for permission prior to submission and publication."*

Therefore:

- *Members should not engage in any act of plagiarism, including self-plagiarism.*
- *Members should not publish any material relating to the activities of an ISPOR Task Force, Special Interest Group or other ISPOR group at any stage, without first consulting fellow group members / co-authors for permission.*

See chapter 5 for more on scientific misconduct.

Bias

A key concern in publication and dissemination is the possibility of bias, either *publication bias*, whereby studies with negative or inconclusive results tend not to be published, or *analytic bias*, whereby analysts make inappropriate methodological choices that favor one treatment option over another. Bias is a particularly pertinent concern in the field of HEOR, where a high proportion of studies are sponsored and where the analyst often has considerable discretion in the choice of methods and assumptions.

ISPOR has published more than 50 Good Practices for Outcomes Research Reports on conducting outcomes research (clinical, economic or patient-reported) or using outcomes research in health care decisions. (Please see ISPOR Good Practices for Outcomes Research Index, https://www.ispor.org/workpaper/practices_index.asp) While these reports do not address ethical principles directly, the specification of good research methods is an important component of recognizing and eliminating analytic bias.

The main method of disseminating HEOR is through peer-reviewed journals. Therefore, a major source of ethical principles and good publishing practice is the recommendations of the ICMJE[39], which have the endorsement and support of all the major clinical and health services research journals (ICMJE, 2016). The recommendations for ISPOR members in this chapter are consistent with those of the ICMJE but offer more details relevant to this particular field of research.

Freedom to Publish the Findings without Restrictions

Both peer-reviewed journals and the users of HEOR take an interest in the nature of the relationship between the researcher and the sponsor, as this is one indicator of the likelihood of any bias in the research. This relationship is usually expressed through a contract between the researcher and sponsor. In negotiating the contract, researchers should pay particular attention to the need for transparency throughout the research process and the freedom to publish the findings without restrictions[40].

Members should seek to establish, in advance, a clear agreement with the sponsor on whether the results of a given piece of work can be published or presented. This could include statements on whether the sponsor has a right to review or approve any manuscript prior to publication and on which party has the intellectual property rights in the outputs of the research. It is important to specify publication rights, one way or the other, in the contract. University contracts usually do specify and generally a university will not sign off on a contract that allows the sponsor to disallow publication. Prior review and comment is generally accepted by universities. Individual researchers or vendors may be willing to do "work for hire" which does not guarantee publication rights; in such a case, if anything is

published, it should be disclosed that publication rights were not guaranteed in advance. Considerations where preventing publication would not be acceptable in any case could include revelations of safety issues, in which failure to disclose could result in a public health hazard.

Therefore:

- In the case of sponsored research, members should agree to a contract that clearly sets out their rights, and those of the sponsor (e.g., intellectual property rights and rights to publish), in the conduct and reporting of the study. The nature of this agreement should be summarized in the published paper.

Transparency in Reporting

Transparency in reporting is also essential to reduce the possibility of bias in research. Several reporting guidelines exist, including those developed by CONSORT for clinical research (including quality of life measurement)[41] [42] [43] [44] and STROBE for observational studies[45]. High-quality reporting also aids the peer-review process, although journal editors and reviewers may also ask for access to the original data, the statistical analyses performed, or the models used in the research.

Authors of publications should endeavor to respond as fully as possible to requests for additional information on their data or methods. Offering full access to data, analyses and models represents a level of transparency that can enhance the credibility of the research. However, access to some data may be restricted by contractual obligations, proprietary reasons, IRB restrictions or the general need to protect the privacy of participants in the research. Also allowing access to executable electronic copies of models has raised specific concerns on the part of researchers who fear that their intellectual capital could be undermined if the model were copied[46].

On the other hand, peer reviewers and journal editors may feel that access is required in order to adequately verify the quality of the research. Researchers should remember that peer reviewers are already bound by confidentiality agreements, and some journals have strengthened these in order to reassure authors that the intellectual capital in their work will be protected.

It was mentioned in Chapter 4 that the registration of the clinical study alongside which a HEOR is conducted can be a key element in ensuring the transparency of research, therefore:

- Where a HEOR study is being conducted alongside a clinical study gathering data prospectively (such as a clinical trial or observational study) members should report whether the clinical study concerned has been registered on ClinicalTrials.gov, Registry of Patient Registries (patientregistry.ahrq.gov), ENCePP e-Register of Studies[47], or equivalent databases of studies in their own country or region.

Where research is disseminated in non-peer-reviewed journals or through electronic media, such as websites or social media, the scrutiny of peer review does not generally exist (although comments sections on web posts might be considered an informal peer review). The way in which researchers should approach this depends on whether they are purporting to report fact or opinion—unless it is clear that mere opinions are being expressed, authors should be willing to offer the same level of access to underlying data and/or analyses as they would to journal peer reviewers.

Study Authorship

The named authors formally take responsibility for the report of the research. Therefore, some study users view the identity of the authors as one indicator of the likely quality and reliability of the research, although when acting as editors or reviewers of papers for journals, ISPOR members should make

judgments based solely on the quality of the research, not the identity or affiliations of the authors (if these are not already anonymized by the journal concerned)

Authorship also provides recognition of the researchers' contribution. Therefore, it is wrong to include an author who did not make a substantive contribution due to their name recognition and perceived status. Similarly, it is wrong to exclude an individual who had made a substantial contribution because of their affiliation. Criteria include:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND
2) Drafting of the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved[48]

Other individuals participating in the research, but not qualifying as authors, should be acknowledged.

In addition, the ICMJE and many peer-reviewed journals require the corresponding author to confirm that these conditions have been met. Specific journals such as JAMA have guidelines, and these are very useful generally.

Journals now generally require individual authors of a manuscript to certify by signature that they have contributed sufficiently to be listed as an author. However, journals vary in their requirements for certification so ISPOR, as an organization, encourages its members to adhere to fair and equitable requirements for authorship and to respect their colleagues in the process.

Financial Disclosure, Conflicts of Interest and Past Work Relationships

Another important condition of authorship is that individuals disclose any financial and/or other relationships that may be perceived to be conflicts of interest with respect to the work being reported. In the field of HEOR, it is particularly important to disclose any present or past relationships with the manufacturers of any products referred to in the research or any competitor products.

In reporting past relationships, many researchers will have a large number of such relationships stretching back over a number of years. A common time frame is to report any relationships within the past three years[49], but different journals have different guidelines. The ICMJE specifies no limit.

Therefore:

- Members should endeavor to publicly disseminate their work and to publish it in peer-reviewed journals when possible.

- Members should work, where appropriate, to encourage the establishment and/or maintenance of an appropriate peer review process that examines the quality of the methodological rigor independently of the organization for which the individual works.

- Members serving as peer reviewers for journals should respect the confidentiality of the material under review and understand that their access to it is solely for the purposes of performing the review.

- The description of study methods (design, study setting, data sources and input values, sampling and analyses) should be complete and transparent enough for a suitably trained researcher to replicate the study.

- Methods sections of papers should give thorough, transparent attention to all measures taken to minimize bias.

- Where allowable by law and IRB approval, members should respond favorably to requests from journal editors and reviewers for access to original data and electronic copies of models where this access is required to ensure a rigorous peer review process and where commercial-in-confidence arrangements can be maintained.

- In those instances in which study methods include analysis of a database (retrospective or prospective), members should describe approaches, methods, technologies used to ensure data completeness, and validity as well as the software package(s) used for data analysis. Members should have the education, training, and experience to perform the assigned tasks.

- In those instances in which sharing of model(s) and/or data source(s) is not feasible, members should be encouraged to provide supporting material demonstrating model and/or data validity, such as range and logic checks, and assessment of data completeness.

- If submitting to a journal or publication that does not have peer review, or disseminating a report via electronic media, members should avoid the inclusion of material that is overly technical and/or cannot be supported by basic article references, or make it clear that the article represents the author's own opinion. If research is being reported, then access to the underlying data and/or analyses should be offered in the same manner as would be done under a peer-review process.

- Members should never intentionally plagiarize another author's work and if publishing work similar to anything jointly authored with others should ensure that no replication of the prior work was unintentionally done.

CHAPTER 9: CONCLUSION AND LIMITATIONS

ISPOR recognizes that within the fast changing climates of different health care systems, it is difficult to address all ethical issues HEOR practitioners face. New data sources might emerge; genomic sequencing and Internet of Things might make privacy almost impossible to protect; and open data might pose new challenges to intellectual property rights.

Nevertheless, ISPOR recognizes that its activities and those of its members affect a number of constituencies, and there may be conflicting standards of professional conduct. Patients as stakeholders and patient engagement are two relatively new concepts impacting health care research, especially in Europe and North America. While the impact of this much needed social movement is slowly starting to become clearer, its relevance and impact on ISPOR members, especially researchers, requires further elucidation and guidance. This Code, however, cuts across virtually all areas of research and dissemination and is meant to be a comprehensive guide for HEOR researchers.

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ISPOR CODE OF ETHICS 2017 SUMMARY POINTS

CHAPTER 1: INTRODUCTION

1. *ISPOR should publicize this Code of Ethics to members and non-members involved in pharmacoeconomics and outcomes research.*

2. *ISPOR should strive for a balance in sponsorship of its conferences and other activities by providing decision criteria for accepting of funding and ensuring full transparency, thereby avoiding the appearance of bias or conflict of interest.*

3. *Because, as a practical matter, most funding will come from different entities, ISPOR should continue to maintain its own statement of objectivity and autonomy.*

4. *ISPOR should strive to assure that its journal, Value in Health, only publishes papers that have gone through a rigorous peer- review process.*

5. *ISPOR should have a Board of Directors that is representative of the various constituencies the Society serves.*

6. *The ISPOR program planning and selection committees should have membership representative of all of its major constituencies.*

7. *Like other professional societies, ISPOR should be conscious of broader ethical issues impacting on global and regional medical resource allocation, public health policies and the global healthcare environment, and the research side on topics such as patient autonomy and research conduct. These issues include but are not limited to: prejudice, equity in healthcare delivery and access.*

CHAPTER 2: APPLICATION OF ETHICAL PRINCIPLES TO THE ISPOR CODE

8. *Members should maintain a current knowledge of research practices, with due consideration of those practices most relevant to the research that is being done in their own countries.*

9. *Privacy: Members who work in HEOR can be privy to data sources containing protected health information (PHI) and other personal data from patients. It is essential that these data are handled with utmost care so that patient confidentiality can be maintained at all times and no breaches to patient privacy occur.*

10. *Transparency and Integrity: Members must disclose research methods in sufficient detail to permit replication. The funding sources should be clearly acknowledged, and any conflicts of interests declared. Designing, conducting and especially reporting of the study should be an unbiased reflection of the full range of findings generated.*

11. *Civility: Members' research and discussion should respect the dignity of all participants, including patients and providers of care. It is also a responsibility to treat fellow researchers with respect.*

CHAPTER 3: SCOPE OF THE CODE

12. *Members should adhere to the standards of practice for their respective fields of research and identify any official guidelines and standards used.*

CHAPTER 4: RESEARCH DESIGN CONSIDERATIONS

13. *When recruiting patients for a study, from the point of "first contact" researchers should be open about their intentions and how the research is funded, and should provide potential subjects with the information mandated in their proposals as reviewed by research ethics committees.*

14. *Members should describe the analytic population in terms of persons, geography, time period and selection criteria. Members should choose, and obtain permissions to use a suitable research setting and/or existing data or literature to provide information about a specific patient population to which the study results are meant to apply. The number of sites selected for a study should be appropriate to meet the research objectives.*

15. *Safety and adverse events reporting (AER) are important aspects of all primary research involving patients and medical interventions, are applicable to many HEOR activities, and must follow international guidelines.*

16. *The balance of risk or harm to benefit for patients must be considered in HEOR studies, and must be communicated to patients via informed consent.*

17. *While an 'incentive', honorarium or remuneration is often necessary to recruit participants into a research study, researchers must ensure that the incentive would not induce participants to accept risks they would not be willing to accept if they were offered a smaller or no incentive. Any such proposed payments are subject to providers' internal compliance guideline and IRB/EC approval, and must be detailed in the research proposal submitted for review.*

18. *When using secondary data sources initially collected for another purpose, HEOR researchers should ensure that intellectual property rights are respected and that all the appropriate permissions have been secured.*

19. *Given the potential for bias in the analysis of secondary data, the most important general ethical principles are those of 'reasonableness' and 'transparency'.*

20. *While registration of observational studies is generally not required at this time, members are encouraged to register such studies prospectively to recognize ethical obligations to patients and to avoid the potential for publication bias.*

21. *When study methods include analysis of a database, members should describe approaches, methods, technologies used to ensure data completeness and validity as well as the software package(s) used for data analysis. Members should have the education, training and experience to perform the assigned tasks.*

22. *Where a HEOR study is being conducted alongside a clinical study gathering data prospectively (such as a clinical trial or observational study),where possible members should ensure that the clinical study concerned has been registered on ClinicalTrials.gov, Registry of Patient Registries (patientregistry.ahrq.gov), ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) e-Register of Studies[†], or equivalent database in their own country.*

23. *In conducting modeling studies, members should: ensure that the input parameters are estimated based on a comprehensive review of the available literature; be transparent about the estimates they use for key parameters; provide the logic they used in selecting particular estimates; and explore the impact of their choices through sensitivity analysis.*

CHAPTER 5: DATA CONSIDERATIONS

24. *When a database (from primary data collection and/or secondary data use) is analyzed, members should provide a description of approaches, tools and technologies used to store the data and maintain patient privacy/confidentiality and de-identification.*

25. *Personal data should be maintained securely and adequate back-up should be maintained. Data access should be limited to authorized individuals. Control systems should be put in place to ensure authenticity, integrity and confidentiality of data records when transmitted electronically.*

26. *Researchers should offer the maximum level of access to the anonymized, group-level data used in their research. If data access is restricted by proprietary or contractual considerations, those considerations should be disclosed. If journal reviewers deem it important that statistical review of proprietary data be conducted, authors should work with both the data owners and the reviewers to find appropriate confidential arrangements for such review whenever feasible.*

27. *Members' hypotheses and research designs should be defined a priori, reported transparently, defended relative to alternatives, and planned to recognize and minimize all types of bias.*

28. *Members should fully disclose the identity of sponsors of their research.*

29. *Members should strive to avoid bias and the appearance of bias in conducting research, such as in the choice of methods and data inputs, or in the selective reporting of results*

30. *Members should be aware of conflicts of interest and the appearance of conflicts of*

[†] encepp.eu/encepp/studiesDatabase.jsp

interest. As a point of reference, members should look to the rules on disclosure of potential conflicts of interest laid down by major peer-reviewed journals and their own institutions.

31. *Members should maintain their professional autonomy and objectivity in conducting and reporting, in writing or verbally, research findings.*

32. *Methods sections of papers should identify and justify all departures from the a priori analysis plan.*

33. *Members should maintain and protect the integrity of data used in their studies as well as on any other aspect of their research, as previously discussed (e.g. respect for patient autonomy such as informed consent and data privacy).*

34. *Members should not draw conclusions beyond or inconsistent with what their data would support and discuss any limitations in a transparent manner.*

CHAPTER 6: SPONSORSHIP AND RELATIONSHIPS WITH OTHERS

35. *Members should respect the reputations and rights of colleagues when engaged in collaborative projects*

36. *Members should treat their research employees with respect and should compensate them fairly for their work.*

37. *Members should protect and promote the interests of their employers, provide competent work, adhering to these broader guidelines, and protect proprietary information.*

38. *Members should treat students with respect and refrain from exploiting them under any circumstances.*

39. *Members acting as sponsors should allow HEOR researchers at all times to maintain their scientific integrity and adhere to relevant standards in conducting and reporting research.*

40. *Members should respect contractual rights when they agree to perform work for hire and should refrain from disseminating information which they agreed in advance to keep proprietary.*

41. *When acting as key opinion leaders (KOLs), ISPOR members should be transparent about payments – and any other benefits - they receive for acting in this capacity.*

42. *When acting as KOLs, ISPOR members should ensure that the information they are presenting is an accurate representation of the facts available. They should respond to questions and queries honestly and to the best of their abilities.*

43. *When relying on KOLs, ISPOR members should critically engage with the claims being made. Where appropriate they should seek independent corroboration of any factual claims and consider the full range of alternatives for themselves.*

44. *When acting as Advisory Board Members, ISPOR members should maintain their independence and professional autonomy and act transparently, e.g., declare conflicts of interest.*

45. *Members should respect the autonomy of research participants in designing and conducting studies, specifically but not limited to informed consent and data privacy.*

CHAPTER 7: PATIENT ENGAGEMENT

46. *Stakeholder input including patients (and representatives of patients such as family caregivers and advocacy organizations) in study development, can strengthen the study design and utility.*

    a. *Patient input is valuable throughout the medical product lifecycle from early development to dissemination and post-marketing surveillance.*

    b. *Researchers should involve patients and their representatives as partners before, during, and after conducting research.*

47. *To prevent or address ethical issues arising in the patient engagement process, following established protocols and guidelines is recommended.*

CHAPTER 8: PUBLICATION AND DISSEMINATION

48. *Members should not engage in any act of plagiarism. Members should not publish any material relating to the activities of an ISPOR Task Force, Special interest Group or other ISPOR group without first consulting fellow group members for permission*

49. *In the case of sponsored research, members should agree to a contract that clearly sets out their rights, and those of the sponsor (e.g. intellectual property rights and rights to publish), in the conduct and reporting of the study. The nature of this agreement should be summarized in the published paper.*

50. *Where a HEOR study is being conducted alongside a clinical study gathering data prospectively (such as a clinical trial or observational study), members should report whether the clinical study concerned has been registered on ClinicalTrials.gov, Registry of Patient Registries (patientregistry.ahrq.gov), ENCePP e-Register of Studies, or equivalent database in their own country.*

51. *Members should endeavor to publicly disseminate their work and to publish it in peer-reviewed journals when possible.*

52. *Members should work, where appropriate, to encourage the establishment and/or maintenance of an appropriate peer review process that examines the quality of the methodological rigor independently of the organization for which the individual works.*

53. Members serving as peer reviewers for journals should respect the confidentiality of the material under review and understand that their access to it is solely for the purposes of performing the review.

54. The description of study methods (design, study setting, data sources and input values, sampling and analyses) should be complete and transparent enough for a suitably trained researcher to replicate the study.

55. Methods sections of papers should give thorough, transparent attention to all measures taken to minimize bias.

56. Members should respond favorably to requests from journal editors and reviewers for access to original data and electronic copies of models where this access is required to ensure a rigorous peer review process and where commercial-in-confidence arrangements can be maintained.

57. In those instances in which study methods include analysis of a database (retrospective or prospective), members should describe approaches, methods, technologies used to ensure data completeness, and validity as well as the software package(s) used for data analysis. Members should have the education, training and experience to perform the assigned tasks.

58. In those instances in which sharing of model(s) and/or data source(s) is not feasible, members should be encouraged to provide supporting material demonstrating model and/or data validity, such as range and logic checks, and assessment of data completeness.

59. If submitting to a journal or publication that does not have peer review, or disseminating a report via electronic media, members should avoid the inclusion of material that is overly technical and/or cannot be supported by basic article references, or make it clear that the article represents the author's own opinion. If research is being reported, then access to the underlying data and/or analyses should be offered in the same manner as would be done under a peer-review process.

60. Members should discourage, where possible, listing of an author on any publication where the individual has not performed substantial work. As a point of reference, members should look to the checklists provided by major peer reviewed journals to assist them in deciding inclusion of authors.

61. Any contributor to a report or publication should disclose any current or past relationships with a company or competitor of any product discussed in the work.

62. Members should never intentionally plagiarize another author's work and if publishing work similar to anything jointly authored with others should ensure that no replication of the prior work was unintentionally done.

CHAPTER 9: CONCLUSIONS AND LIMITATIONS

No summary points included

ISPOR CODE OF ETHICS 2017 GLOSSARY

AER – Adverse Event Reporting
AHRQ – Agency for Healthcare Research and Quality
APPI – The Act on the Protection of Personal Information
CMS – Center for Medicare and Medicaid Services
CONSORT - Consolidated Standards of Reporting Trials
COPE – Committee on Publication Ethics
CRO – Clinical Research Organization
EC – Ethics Committee or Research Ethics Committee
EFPIA – European Federation of Pharmaceutical Industries and Associations
ENCePP – European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GDPR – General Data Protection Regulation
HEOR – Health Economics and Outcomes Research
HIPAA – Health Insurance Portability and Accountability Act
HTA – Health Technology Assessment
ICH GCP – International Conference on Harmonization Good Clinical Practice
ICJME – International Committee of Medical Journal Editors
IoT – Internet of Things
IRB – Internal Review Board
KOL – Key Opinion Leader
PHI – Protected Health Information
REC – Ethics Committee or Research Ethics Committee
SEER – Surveillance, Epidemiology and End Results
SNIIRAM – Systeme National d'Information Inter Regimes de l'Assurance Maladie
STROBE - STrengthening the Reporting of OBservational studies in Epidemiology.
TPP – Target Patient Profile
UK HES – United Kingdom Hospital Episode Statistics

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