

**ISPOR Code of Ethics 2017 (4th Edition)**

**APPENDICES**

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## **APPENDIX 1          Summary of Previous ISPOR Codes of Ethics**

In 1997, ISPOR set up a number of discussion panels to deliberate on issues arising in the field. One was asked to study questions about bias, credibility, and quality of health economic evaluations. This panel presented its conclusions during the Society's 1998 meeting. These conclusions were subsequently published in *Value in Health* in 1999.<sup>1</sup>

One of the panel's recommendations was establishment of an ISPOR Code of Ethics. The authors felt that such a code would help the fledgling pharmacoeconomics and outcomes research disciplines deal with credibility challenges stemming from concerns about methods or bias. The objective was establishment of procedures for proper and ethical research design, conduct and reporting so that stakeholders and constituencies could trust and benefit from HEOR study findings.

A task force was initiated and ISPOR's first formal Code of Ethics for Researchers was published in *Value in Health* in 2004.<sup>2</sup>

In a letter to the editor<sup>3</sup> and in an editorial<sup>4</sup> both published in *Value in Health* in 2004, ISPOR received legitimate criticism of its first code. One major issue related to the lack of representation from countries outside the U.S. While the Task Force did have some representation, this was expanded for the new review.

The ISPOR Board of Directors considered the comments received, initiated a review of the Code with the reassembled task force subsequently addressing these concerns in a new Code of Ethics,<sup>5</sup> published in *Value in Health* in 2009, covering principles on design and research, sponsorship, publication and dissemination, relationship with others and role of ISPOR.

## APPENDIX 2            Other Existing Codes of Ethics Relevant to HEOR

A non-exhaustive summary of Guidelines/Standards/Codes referenced for the ethical conduct of HEOR is summarized here.

### 2.1 International Guideline/Codes

#### 2.1.1 The Declaration of Helsinki

In 1947, the World Medical Association (WMA) was formed as an open forum to discuss medical ethics, medical education, socio-medical affairs and medical topics generally. In 1964, the WMA drafted the Declaration of Helsinki<sup>6</sup>, recognized as the ethical foundation for biomedical research.

#### 2.1.2 The Belmont Report

The Belmont Report<sup>7</sup> was prepared in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report explains the three fundamental ethical principles that form the basis for the National Commission's topic-specific reports and the regulations that incorporate its recommendations.

**Respect for persons:** protecting the autonomy of all people and 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 subjects; 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.

Application of these principles requires careful consideration of informed and voluntary consent, risks and benefits, and the selection of participants for research.

#### 2.1.3 International Conference on Harmonisation Good Clinical Practice (ICH GCP)

In 1996, the harmonized tripartite guideline for good clinical practice ICH GCP was adopted in Europe and in 1997 in the USA and Japan<sup>8</sup>. This began the process for harmonizing the ethical and scientific quality standards for clinical trials. However, there remains disparity in ethical and scientific quality standards for research not classified as clinical trials, including that conducted for HEOR, among the three ICH regions.

#### **2.1.4 International Society for Pharmacoepidemiology (ISPE) Guideline for Good Pharmacoepidemiology Practices (GPP)**

Ethical issues, data ownership and privacy are considered as part of the ISPE Guideline for GPP<sup>9</sup>, most recently updated in 2015. The GPP are intended to apply broadly to all types of pharmacoepidemiology research, including therapeutic risk management and comparative effectiveness research. The Guideline for GPP does not replace, but is complementary to, the Guideline for GCP, providing guidance of specific relevance to non-interventional studies.

#### **2.1.5 International Epidemiological Association (IEA) Good Epidemiological Practice (GEP) Guidelines**

The IEA GEP Guidelines<sup>10</sup> outline the background to epidemiological research and the role of ethics committees. General ethical principles for research are consistent with the Belmont Report. The Guidelines provide additional direction on working with personal data, data documentation, publication, and exercise of judgment with a final note on scientific misconduct.

#### **2.1.6 The Council for International Organizations of Medical Sciences (CIOMS)**

The Council for International Organisations of Medical Sciences (CIOMS)<sup>11</sup> 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects<sup>12</sup> was prepared in collaboration with the World Health Organization (WHO). The guidelines consist of a statement of general ethical principles for the conduct of biomedical research involving human subjects, and are of particular relevance to low income settings. The CIOMS 2009 International Ethical Guidelines for Epidemiological Studies<sup>13</sup> set forth ethical guidance on how investigators - as well as those who sponsor, review, or participate in the studies they conduct - should identify and respond to the ethical issues that are raised by such research. In 2010 the Executive Committee of CIOMS decided to revise the CIOMS Ethical Guidelines for Biomedical Research which is open for public consultation<sup>14</sup>.

#### **2.1.7 The United Nations Educational, Scientific and Cultural Organization (UNESCO) Bioethics Programme<sup>15</sup>**

UNESCO acts as a forum for multidisciplinary, multicultural and pluralistic ideas on bioethics and on the ethics of science and technology. The International Bioethics Committee (IBC), created in 1993, is a permanent committee comprising 36 independent experts. IBC promotes reflection on the ethical and legal issues raised by research in the life sciences and their applications to ensure respect for human dignity and freedom. It is the only global mechanism of its kind. The World Commission on the Ethics of Scientific Knowledge and Technology (COMEST) is an advisory body and forum of reflection. The Commission is mandated to formulate ethical principles that could provide decision-makers with criteria that extend beyond purely economic considerations.

## **2.2 Regional or Country Specific Guidelines/Codes**

### **2.2.1 The Agency for Healthcare Research and Quality (AHRQ)<sup>16</sup> of the United States**

The Agency for Healthcare Research and Quality (AHRQ) published Registries to Evaluate Patient Outcomes: a User's Guide, Third Edition, 2014<sup>17</sup>. The guide is intended to support the design, implementation, analysis, interpretation, and quality evaluation of registries created to increase the understanding of patient outcomes. Section II of the guide covers legal and ethical considerations for registries including the principles of registry ethics, data ownership and privacy, informed consent, and the protection of data.

### **2.2.2 European Directives and Guidance**

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) summarizes European guidance for ethical conduct, patient and data protection in the Guide on Methodological Standards (Revision 4)<sup>18</sup>. Standards for trials that involve human subject participation have been adopted through a number of Directives. Marketing authorization holders and investigators must also follow relevant national legislation and guidance of those Member States where the study is being conducted.

The ENCePP Code of Conduct<sup>19</sup> was adopted in 2010 to maximize transparency and to promote scientific independence throughout the research process of pharmacoepidemiology and pharmacovigilance.

### **2.2.3 The European Federation of Pharmaceutical Industries and Associations (EFPIA)**

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. The EFPIA Disclosure Code<sup>20</sup> is a code of conduct that requires all EFPIA member companies and companies that are members of EFPIA member associations to disclose transfers of value to healthcare professionals and healthcare organizations. EFPIA provides a summary of European National Codes of Conduct<sup>21</sup>.

### **2.2.4 The European Society for Opinion and Market Research (ESOMAR)<sup>22</sup>**

The ICC (International Chamber of Commerce)/ESOMAR Code on Market and Social Research sets out global guidelines for self-regulation for researchers and has been undersigned by all ESOMAR members and adopted or endorsed by more than 60 national market research associations worldwide. The Code sets minimum standards of ethical conduct to be followed by all researchers and clients and is to be applied against the background of applicable law and of any stricter standards or rules that may be required in any specific market.

### **2.2.5 The UK's Economic and Social Research Councils Framework of Research Ethics**

The UK's Economic and Social Research Council's (ESRC) Framework for Research Ethics (FRE) was first published in 2002, with the most recent substantial revision in February 2016.<sup>23</sup> It includes instruction to those who conduct social scientific research in the domain of pharmacoeconomics, and offers guidance on many of the ethical issues that can arise throughout the research lifecycle. The FRE is easy to consult and navigate, and is hosted on a website for ongoing updates.

### **2.2.6 Guidelines for Research Ethics in China**

The UK Medical Research Council has summarized guidelines for research ethics in China comparing these to the UK<sup>24</sup>. Chinese laws and guidelines cover many aspects of medical research and are evolving rapidly. Chinese guidelines draw extensively on international guidance, such as ICH GCP. Underlying ethical principles governing the conduct of medical research in China are broadly similar to the UK although there are particular challenges, for example, interpreting individual informed consent in a culture that places high value on family involvement in decision making. However, some aspects of medical research are much more closely regulated in the UK than in China, such as uses of human tissues and data protection.

### **2.2.7 The RESPECT Code of Practice for the Conduct of Socio-economic Research**<sup>25</sup>

The RESPECT guidelines are intended to form the basis of a voluntary professional and ethical code of practice covering the conduct of socio-economic research in Europe. The RESPECT code of practice is based on three main principles: Upholding scientific standards; Compliance with the law; Avoidance of social and personal harm.

### **2.2.8 Guidelines for Research Ethics in Japan**

In Japan, there are two governance systems for clinical and epidem

iological research, depending on the intended use of the study results. The Pharmaceutical and Medical Device Act applies to studies intended for regulatory submission for market authorization. Sponsors should comply with the Ordinance of the Good Post-market Study Practice (GPSP) for Japanese post-marketing surveillance. The GPSP Ordinance and the relevant regulatory documents lack any provisions on ethical aspects including ethical review and participant protection. For studies not intended for marketing authorization, non-statutory "Ethical Guidelines for Medical and Health Research involving Human Subjects" are applicable<sup>26</sup>. These non-binding guidelines entail ethical review of all research involving human participants and samples regardless of the type of study design, and give advice on the level of participant protection such as the requirement for informed consent.

### **2.2.9 The Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Subjects<sup>27</sup>**

The Indian Council of Medical Research developed the 'Ethical Guidelines for Biomedical Research on Human Subjects' in 2000. They were revised in 2006. These guidelines have elaborated the three basic ethical principles: respect for person, beneficence and justice by inducting twelve general principles. These concepts hold special importance in developing countries, such as India, where many of the research participants are uneducated and of low socio-economic status.

## **2.3 Patient Engagement Resources**

### **2.3.1 Adherence and Concordance: European Patients Forum Position Paper**

The European Patients Forum (EPF) published a position paper focused on effective use of medicines as part of self-management of chronic conditions in March 2015.<sup>28</sup> Non-adherence to prescribed medicines has a large impact on patients and health care systems. The paper describes the different terminology used, with recommendations for use of terms such as adherence and concordance. Adherence implies a more active role: collaboration with the health care professional with no blame. Concordance is a more recent term that describes where beliefs of the health care professional and the patient are involved, representing a shared decision and a link to patients' personal treatment goals. In addition, the paper describes rationale for non-adherence and strategies to support patient adherence, role of patient organisations and policy recommendations for EU & national policy makers, researchers and stakeholders. The EPF was founded in 2003 to ensure that the patient's community drives policies and programmes that affect patients' lives to bring change, empowering them to be equal citizens in EU.

### **2.3.2 Patient Involvement in Clinical Research: A guide for Sponsors and Investigators. A guide for Patient Organizations and Patient Representatives. Produced by the Patient Partner project funded by the 7th Framework Program of the European Commission. Genetic Alliance UK, April 2011 (ref: 201720)<sup>29</sup>**

This guide to patient involvement in clinical research was made available, after 2011 for investigators and sponsors of research wishing to develop meaningful partnerships with patients and patient organisations. The inventory of the existing views, needs, practices and experiences of patients, forms the basis of the Patient Partner project which aims to identify patient needs for partnership in the clinical trials context. Partners working on this project included: the European Forum for Good Clinical Practice (EFGCP), the European Genetic Alliances Network (EGAN), Genetic Alliance UK and the Dutch Genetic Alliance (VSOP). A similar guide was also developed for patient organisations and patient

representatives.

### **2.3.3 National Health Council & Genetic Alliance. Dialogue/Advancing Meaningful Patient Engagement in Research, Development, and Review of Drugs. September 2015**

The National Health Council and Genetic Alliance, convened a Dialogue Event at the offices of the Food and Drug Administration (FDA) as part of the broader effort to advance patient engagement in the research, development, and approval of medical products in the USA. By providing a forum for thought leaders to share their perspectives, experiences, and expertise, the National Health Council and Genetic Alliance hoped to establish a common vision that would help drive meaningful integration of the patient voice in the product development and approval processes. Key aspects that need to be addressed included regulatory/legal uncertainty, culture shift among organizations and increasing communications especially within the public domain.

### **2.3.4 Clinical Trials Transformation Initiative (CTTI): Effective Engagement with Patient Groups around Clinical Trials.**

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership that develops and drives adoption of practices that will increase the quality and efficiency of clinical trials. It was established in 2007 through a partnership between the FDA and Duke University, and is administered through the Duke Translational Medicine Institute. This guidance document includes a road map on how to engage with patient groups regarding clinical trials especially for pharmaceutical companies and academic institutions.

## **2.4 Publication Ethics Codes**

### **2.4.1 The International Committee of Medical Journal Editors (ICJME)<sup>30</sup> Uniform Requirements for Manuscripts Submitted to Biomedical Journals**

The ICMJE is an independent group of medical journal editors that developed recommendations for conducting and reporting accurate, clear, reproducible and unbiased medical journal publications. It states ethical principles related to publication in biomedical journals are included in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals by the International Committee of Medical Journal Editors (ICJME)<sup>31</sup>. The requirements cover authors, contributors, editors, peer review, conflicts of interest, privacy and confidentiality and the protection of human subjects and followed by more than 600 medical journals worldwide.

ICMJE has substantive contribution to authorship that begins from the study conception until the proof reading, aims to prevent gift authorship and ghost writing. HEOR is usually a collaborative work across disciplines that involved increasing number of scientists that play various role in the project. There are many trial based economic evaluations, where the trial center sole role as



sample contributor will not qualify them as author. Therefore, there may be a role for a more pragmatic approach to authorship, based on contribution instead of strictly fulfilling all six authorship criteria by ICMJE.

#### **2.4.2 The Committee on Publication Ethics (COPE)<sup>32</sup>**

The Committee on Publication Ethics (COPE) aims to define best practice in the ethics of scholarly publishing and to assist editors, editorial board members, owners of journals and publishers to achieve this. In 2011, COPE published their Code of Conduct and Best Practice Guidelines for Journal Editors<sup>33</sup>. The COPE Code of Conduct for Journal Editors is designed to provide a set of minimum standards to which all COPE members are expected to adhere. The Best Practice Guidelines are more aspirational and were developed in response to requests from editors for guidance about a wide range of increasingly complex ethical issues. While COPE expects all members to adhere to the Code of Conduct for Journal Editors, the Best Practice recommendations are voluntary.

#### **2.4.3 American Economic Association**

The American Economic Association (AEA) requires that submissions to AEA journals should conform to the AEA disclosure principles set forth in its disclosure policy.<sup>34</sup> Disclosure is required of a broad range of interested parties (including financial, ideological and political association), any paid or unpaid positions and the right to review. The author(s) must disclose whether they have obtained Institutional Review Board (IRB) approval for papers involving the collection of data on human subjects, or reasons for an IRB waiver should be stated. The AEA urges its members and other economists to apply these principles across a range of publication types including scholarly journals, newspaper and magazine columns, radio and television commentaries, as well as in testimony before agencies.

## APPENDIX 3 HEOR Related Common Research Types

### 3.1 Clinical Trial / Study

According to ICH GCP<sup>5</sup>, a clinical trial /study is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. Per ICH GCP glossary<sup>35</sup>, the terms clinical trial and clinical study are synonymous.

However, for the purposes of implementing section 901 of FDA Amendments Act (FDAAA)<sup>36</sup>, clinical trials and studies are defined differently: Clinical trials are any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human participants. Clinical studies are all other investigations with humans that are not clinical trials as defined above, e.g., observational epidemiologic studies, animal studies, and laboratory experiments.

Regulation (EU) No 536/2014 of the European Parliament and of the European Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC<sup>37</sup> put forth new definitions of clinical studies and trials. 'Clinical study' means any investigation in relation to humans intended: a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; b) to identify any adverse reactions to one or more medicinal products; or c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products.

'Clinical trial' means a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the participant in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

The Japan GPSP Ordinance categorizes commercial post-marketing studies sponsored by marketing authorization holders (MAHs) into two classifications: Drug Use-Results Surveys and Post-Marketing Clinical Trials. However, classification by study design and definitions of intervention and observational studies are provided in neither the GPSP Ordinance nor the supplementary guidelines for post-marketing studies.<sup>38 39</sup>

### 3.2 Non-Interventional Trial / Study

Regulation (EU) No 536/2014<sup>7</sup> defines a 'non-interventional study' as a clinical study other than a clinical trial (as described by the same EU regulations above). A non-interventional trial is

defined in Article 2(c) of Directive 2001/20/EC as follows: “a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

### **3.3 Real World Data**<sup>40</sup>

Real world data (RWD) is an umbrella term for data regarding the effects of health interventions, e.g. benefit, risk, resource use, etc., that are not collected in the context of conventional randomized controlled trials. Instead, RWD is collected both prospectively and retrospectively from observations of routine clinical practice. Data collected include, but are not limited to; clinical and economic outcomes, patient reported outcomes (PRO) and health-related quality of life (HRQoL). RWD can be obtained from many sources including patient registries<sup>41</sup>, electronic medical records, claims files and observational studies.

### **3.4 Real World Evidence**

Real World Evidence (RWE) is the evidence derived from the analysis and/or synthesis of real-world data (RWD).<sup>42</sup>

### **3.5 Real World Research Study**

A real world research study refers to all clinical studies investigating health interventions whose design does not follow the design of a randomized controlled clinical trial and aims to reflect health intervention effectiveness in routine clinical practice. Real world studies do not typically include randomization of trial subjects, but there are exceptions (e.g. pragmatic clinical trials).<sup>43</sup>

Real world studies include, but are not limited to, the following:

- pragmatic clinical trials,
- prospective observational (i.e. non-interventional) studies
- retrospective observational (i.e. database) studies,
- retrospective observational database analyses, which could be exploratory/ non-confirmatory by nature or for hypothesis generation only
- drug utilization studies,
- post-authorization efficacy/safety studies (Adapted from IMI-GetReal, 2014).

Researchers use real world evidence to address challenges related to product performance, clinical outcomes, risk and safety, and access and reimbursement, including Non-Interventional Studies (NIS), Disease focused Observational Studies, Epidemiology Studies, Pharmacoepidemiology Studies and Health Economics Outcome Research (HEOR). An

ongoing initiative of EMEA is to include patient input into the development and collection for real world evidence, after the marketing authorization.

### **3.6 Market Research<sup>44</sup>**

Market research is the systematic gathering and interpretation of information about individuals or organizations using the statistical and analytical methods and techniques of the applied social sciences to gain insight or support decision making. The identity of participants will not be revealed to the user of the information without explicit consent and no sales approach will be made to them as a direct result of their having provided information. Market research is not a commercial communication or a selling opportunity and has no interest in the individual identity of participants.

Market research (as defined above) relating to market or consumer behavior of the sort that the healthcare industry routinely conduct, whether involving healthcare professionals, patients, careers or members of the public does not require Clinical Research Ethics Committee or Independent Review Board approval (Institutional Review Board in the USA) according to Market Research Associations.<sup>45</sup> Academic and other research institutions may require approval before allowing the research to proceed.

Increasingly market research techniques are used in patient surveys and social media data collection by some researchers and patient organizations. These usually form the basis for disease burden reports and testimonials. Researchers working in this space are strongly encouraged to also collaborate with patient organizations to identify key topics of interest, recruitment via their members, interpretation of the findings, how best to communicate these and to whom. Reassuringly, these types of research tend to be better able to highlight topics and issues that are relevant and important to patients and their families.

## APPENDIX 4                      Examples of HEOR Data Sources

HEOR can utilize multiple data sources in the study. Examples include:

1. Data collected from participants directly, e.g. patient self-reported data, ICF from patients.
2. Patient charts collected from HCPs
  - a. Charts involving personal identifiable data will need patients consent or IRB/EC approval
  - b. Charts involving anonymised data only might be provided by the HCPs with approval from their institutions if necessary according to study type.
  - c. ICF from physicians
3. Secondary literature review
4. Systematic review/evidence synthesis
5. Elicitation
6. Secondary database review, e.g. claims database, EMR database, routine data source, proprietary database, etc.
7. Data mining or data merging from research institutions' existing database
8. Observation data including mystery shopping
9. Social media<sup>46</sup> scraping. Example sources are as follows:
  - a. Online forums/discussions, communities, blogs, social networks (e.g. Facebook)
  - b. Video/photo sharing (e.g. YouTube)
  - c. Multi-person/group communication and/or collaboration platforms (e.g. Twitter).
10. Flow of data from Internet of Things (IoT) and wearables.

When conducting social media research, researchers are bound by the terms and conditions attached to access of the online services and important methodological, ethical and legal considerations.<sup>47</sup>

Quotations containing personally identifiable information (PII) can only be provided to the third party if the contributor has given their consent for this and it has been made clear that they will not be subject to sales or promotion as a result of this.<sup>48</sup>

In 'private' social media spaces (ones in which users would expect their comments to be private), researchers should seek and gain the consent of contributors to listen in/scrape comments, and comments given to clients must be masked unless the contributor gives consent for their comments to be passed on verbatim. This assumes the terms and conditions have not given explicit site owner and site user consent for listening in/scraping<sup>49</sup>.

## **APPENDIX 5            Primary Research Means of Recruitment**

### **5.1    Sample Frame Generation**

Participant lists used for sample frame generation that are drawn from publicly available sources do not generally require the consent of the individuals listed to have their personal details held (all of the data must be drawn from the public domain).

Explicit consent to pass on personal details must be sought when required by local law/regulations. When a list containing personal data that is not in the public domain, if a contractual relationship exists (e.g. Sponsor to CRO) and participants have given prior consent to be contracted for specific purpose, then this does not require the consent of the listed individuals to be contacted. Consent for participation to the specific study will still need to be granted.

#### **5.1.1    Patient Engagement Perspectives**

Researchers may need to consider how to address patient heterogeneity when trying to implement the patient engagement concept. Attempting to have representative sample for patient engagement may require a large sample size which may not be feasible. Suggestions on how to address these are reported in the literature.<sup>50</sup>

#### **5.1.2    Sample Database Management**

When lists of named individuals are used for sample selection, the source of the list should be revealed to potential participants.

Personal data can be added to the database only if the participant is told of this intention at the time of data collection except forbidden by local privacy legislation such as in Germany. Respondents must be told for what purposes the data will be used, and that under no circumstances will it be released or used for any purpose other than the research intended.

Participants have the right to request the deletion of any or all of their personal data from the database at any time and must be respected.

Study sample databases must be returned to the data controller or destroyed at the end of the project.

### **5.2    Recruitment from Databases**

The sample can be recruited from a sample frame or a database generated for the study. The need to contact individuals to solicit their consent may or may not be a prerequisite for accessing data stored in a database. In all cases researchers should follow the regulatory frameworks attached to such sources of data and that are relevant to the context (usually national) in which they are being accessed.

### **5.3 Physician Recruitment of Patients**

Physicians may act as intermediaries (or 'gatekeepers') in the recruitment of research subjects by inviting their patients to take part in proposed research on behalf of researchers or a research agency. Physicians can be part of the research team or participants themselves (e.g. report on observational findings and opinion based input). Physicians recruiting patients must however:

- a. Clearly state their role in the research (e.g., third-party recruiter, trial investigator, their interest or personal benefit of the study)
- b. Clearly state the difference and relationship between research or trial and their standard care treatment.
- c. Ensure that patients understand that their participation is entirely voluntary, and that their care will not be affected by their decision to participate or not participate in the research.
- d. Not disclose the patient's identity to the agency until the patient has consented to this.
- e. Not pressure patients to participate in any study. It is recommended physicians can act as an informer, but not as a trial recruiter. A firewall between the trial coordinator and the participant's physician is important.

#### **5.3.1 Patient Engagement Perspectives**

In Canada and some other countries, physicians are allowed to inform about, but not allowed to actively recruit, their patients into clinical trials at their site. In order to separate clinical care and participation into clinical trials, patients can contact a study coordinator to decide if they are willing to participate.

### **5.4 Snowballing – Participants Supply of Potential Participants' Names**

'Snowballing' is a technique when individuals are asked to supply the names of other people for the purposes of developing a list from which to draw a sample (often used to identify opinion leaders). The person being recruited must be told how their name was obtained to meet the obligation to be transparent. For example, when trying to recruit an opinion leader the recruiter must tell the doctor that they were suggested by another physician. It is not necessary to name the source of the nomination unless agreed by the referees.

### **5.5 Social Media Recruitment**

Researchers may place adverts on social media or use social media platform for recruitment, providing the following are implemented.

- a. Researchers must declare their presence; they must not represent themselves as anything other than researchers.
- b. Contributors should be told the identity of the research organization, purpose of the research, what data will be collected, how their comments will be used and who will have access to it (including all 3<sup>rd</sup> parties and other social media site users).
- c. Contributors should be provided with contact information for the researcher or research agency.

- d. Researchers should publish a privacy policy on their website.
- e. Consent from the site/service owners and contributors/users must be given.
- f. Researchers must disclose their pharmacovigilance reporting policy.

5.6 **Patient Organizations**

Patients and patient organizations have valuable insights and suggestions on how to enlist and retain trial participants.<sup>51</sup> These include access to patients through newsletters, meetings, emails and can identify pitfalls in trial designs and logistics barriers such as number and length of visits, number of test required, location, clinic hours, need for time off work, day care, honoraria and parking. They are also able to provide insights on the daily challenges in living with a specific disease. Generally, most researchers are healthy individuals and understanding these patients' insights can help shape their approaches to their work.



## **APPENDIX 6 Patient Safety and the Reporting of Adverse Events**

### **6.1 Definition**

Adverse Events are defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.<sup>52</sup> An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.<sup>53</sup>

Adverse reactions are defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors. Plus:

- Suspected or confirmed falsified product or quality defects
- Suspected transmission via a medicinal product of an infectious agent
- Misinformation in the product information
- Use of a medicinal product during pregnancy or breastfeeding
- Lack of therapeutic effect . . . unless the reporter has specifically stated that the outcome was due to disease progression
- For vaccines , cases of lack of therapeutic effect should be reported
- Drug interactions – drug/drug, drug/food, drug device and drug/alcohol

### **6.2 Reports without Adverse Reactions**

Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with NO associated adverse reaction are not in the scope to be reported as Individual Case Safety Reports (ICSRs). However, they should be considered in periodic safety update reports as applicable.

### **6.3 Minimum Reporting Criteria**

A valid ICSR should include all following data elements

1. At least one identifiable reporter,
2. At least one single identifiable patient,
3. At least one suspect adverse reaction and
4. At least one suspect medicinal product.

Researchers should identify events based on the information cited, they are not required to probe for missing reporting criteria.

### **6.4 Reporting Timetable**

According to GVP, the clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the national or regional PV center of a competent authority or of any personnel of the MAH, including medical

representatives and contractors. This date should be considered as day zero. In practice this is the first business day the receiver becomes aware of the information.

### **6.5 Reporting Responsibility**

Any personnel of the marketing authorization holder (MAH), including medical representatives and contractors should forward AEs to MAH's pharmacovigilance department.

It is not the responsibility of the researchers to decide on causality between the event and the drug, or whether an event is serious and non-serious, or duplicated events. It is the responsibility of the MAH's pharmacovigilance department to make the final decision.

MAHs have no obligations [to collect AEs] if the program is not commissioned, financed or influenced by them, e.g. syndicated offering from research agencies. In this example, GVP VI does not apply, since it concerns only MAHs and Competent authorities in the EEA. However local requirements may be applicable to the organization who is conducting the program. ISPOR members shall check directly with the competent authorities of the Member State where the program is conducted.<sup>54</sup>

## **APPENDIX 7            Incentive and Disclosure Requirements**

An incentive or honorarium is expected to be provided to the following parties participating in the study as fee for service or compensation for the time involved:

1. Patients, including individuals, carers and members of patient organizations and patient leaders/advocates/experts
2. Healthcare professionals (HCP) including nurses and pharmacists
3. Payers/KOLs and public sector employees
4. Healthcare administrators, e.g. office managers, secretaries, logistic managers, and laboratory researchers
5. Study sites

In general, the following rules will be observed: Dependent only on the active and correct participation of the study

- Kept to a minimum
- Appropriate to the time involved
- No more than the fair market value for that individual's professional consultancy or advice
- Appropriate to the participant type and the task(s) performed
- Payment for physicians is related to compensation for their time
- Local regulations on payment to public employees must apply

### **7.1 Incentives for Patients**

For patients enrolled in clinical trials, it has now become established that out-of-pocket costs should be covered through a lump sum honorarium and not by having to keep track of specific expenses and submitting expense claims.

Patient representatives who provide advice and feedback on clinical trials, irrespective of their development and completion stage, surveys, or a review of documents should be compensated with an honorarium. Often there is national guidance for honoraria and incentives.

Researchers are encouraged to check for any disclosure reporting requirements. It is now expected that researchers plan and budget for this.

Participants should be made aware of the approximate level of commitment and/or length of time required before the incentive will be paid. Incentives provided to HCPs can be perceived as taxable income based on each country's income tax legislation and is usually declared by the individual HCPs.

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.<sup>55</sup>

### **7.2 Incentive Disclosure Requirements**

US Sunshine Act<sup>56</sup> and EU EFPIA's Disclosure Code<sup>57</sup> require payment disclosure between the

healthcare professional and the pharmaceutical industry / patient organizations. Disclosures MUST comply with the national (EFPIA member) code of the country where the HCP receiving payment has their principal practice, such as Loi Bertrand in France<sup>58</sup>.

The Disclosure Code applies to prescription only medicines and only to over the counter medicines if they are dispensed on prescription. Consequently pharmaceutical companies will need to disclose payments made to healthcare professionals (HCPs) for a range of activities including participation in research activities when (and only when) the pharmaceutical company is aware of the identity of the HCP. These payments are referred to in the Disclosure Code as Transfers of Value (ToV).

In clinical or RWR studies where the pharmaceutical Sponsor is aware of the HCP's identities through contractual agreement, disclosure is required.

Research disclosure is required when pharmaceutical companies are aware of the identities of those participating in the study it has commissioned and ToVs, i.e., research-related payments (incentives and expenses) have been made to HCPs. In these cases the payments made to individual named HCP participants must be disclosed.

National data protection legislation may require the HCP's permission for their data to be used in this way. If this permission is not given, payments MUST still be disclosed, but on an aggregate basis. Therefore, if HCP participants do not consent to their personal data being used for disclosure they may still participate in the study, and report will be made on aggregated or anonymized format. In the US, physicians are required to disclose.

If the HCP's identity is not known to the pharmaceutical company disclosure is not required by Sunshine Act and EFPIA. That said, if payment is made and the identity is known, then therefore, must be disclosed.

Pharmaceutical companies must complete and post the disclosure data on their company website or forward it to a central platform – as required in their country.

## **APPENDIX 8            Data Protection Considerations**

Data protection should be considered in all types of HEOR, including both primary and secondary data source and regardless data collection methods and sources, e.g. paper, telephone, online, observational, etc. (see Appendix 4)

### **8.1    Personal Data**

The EU General Data Protection Regulation (GDPR)<sup>59</sup> and the Privacy Shield Network consisting of EU-U.S. and Swiss-U.S. Privacy Shield Frameworks Principles<sup>60</sup> cover the collection of data relating to an identifiable person. The network provides companies with a mechanism to comply with data protection requirements when transferring personal data from the European Union and Switzerland to the United States.<sup>61</sup> (and Japan's regulation on the protection of personal information covers the collection of data relating to an identifiable person in Japan.<sup>62</sup>

These data are referred to as personal data or personally identifiable information (PII). Personal data include postal codes, cell phone numbers and email addresses as well as full names and postal addresses. Personal data may be a single piece of information or a series of pieces of information including other information or datasets available to the holder, which together would allow identification of an individual.

An IP address might constitute personal data in combination with other identifiable data but there is no international consensus about the status of IP addresses (which can generally identify a unique computer, but may or may not identify a unique user). If national law/regulations classify IP addresses as personal data and it is not possible to differentiate between those IP addresses, those that are linked to an individual and those that are not, all the information collected should be treated as if it were personal data.

### **8.2    Data Protection and Privacy**

For data protection purposes original holders of personal data can, if contractually bound, pass personal data to other parties without seeking the explicit permission of the individuals as long as the data is being used for a purpose for which the original holder has a lawful basis to process the personal data, including the consent of the individual.

### **8.3    Processing of Personal Data**

The "processing" of personal data includes the collection, recording, organization, storage, alteration, retrieval, use, disclosure, dissemination, alignment or combination, blocking, erasure or destruction, of personal data.

The processing of "personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life" is forbidden unless one or more of the exceptions specified in the GDPR or the Privacy Shield Principles have been met.<sup>63</sup>

The most important exception is where the participant has given his/her explicit consent to the processing of such data. Explicit consent refers to a participant's specific and unambiguous agreement based upon adequate information.

#### **8.4 Security**

Researchers are responsible for the safe handling, processing, storage and disposal of the research and personal contact data.

Adequate precautions must be taken to protect personal data, any sensitive data and confidential information against unauthorized access. This would include using the appropriate technologies to protect data stored on websites or servers and when data is transferred, e.g., reliable encryption systems, firewall and user identification and password access.

#### **8.5 Storing Agreements about Access to Personal Data**

It is good practice for researchers to keep copies of e-mails, Informed Consent Forms (ICF) and other documents received from participants agreeing to, or restricting, the use of or access to their personal information. This is a legal requirement in some countries, including all European Union member states and U.S. companies that participate in the US-EU Privacy Shield Framework.

#### **8.6 Protection of Personal Data When Transferred**

Personal data are protected by the provisions of the GDPR/Privacy Shield Principles even when taken out of the country where the participant lives.

If personal data are to be transferred from one country to another, the data protection requirements of both countries must be met. The transfer of personal data to non-EU countries is forbidden unless there is adequate privacy protection and specific data protection contractual arrangements in place.

There are various ways in which to comply with the GDPR in non-EU countries depending upon the circumstances. These include Model Clauses and Binding Corporate Rules (BCR)<sup>64</sup>.

In addition, contract research organizations (CROs) may not transfer participants' personal data to any third party without the explicit consent of the participants.

#### **8.7 Participants' Rights to Their Personal Data**

Participants MUST be made aware that they can ask at any time what personal data about them are currently being held and for these to be amended or destroyed.

Increasingly there is collection of biopsy and/or genetic data for screening and treatment in both cancer and non-cancer diagnoses and treatment decisions and/or rare diseases. The European Patient Forum has requested regulation that protects patients' rights as data subjects and as owners of their health and genetic data, and contains measures to enable patients to benefit

from these rights effectively, e.g., right to be forgotten, right to access, right to data portability, right to information and transparency.<sup>65</sup>

Any restriction due to the special nature of the data processed or legitimate reasons for processing of such data should be justified and limited to what is necessary for public health or the patients' vital interest.

Cancer patients and survivors are strongly advocating for access to their biopsy data because they may influence their current or future treatments. These are often collected within clinical trials, where patients may unknowingly abdicate their rights to have access to biopsy data that may have been kept in a centralized location/entity.

To ensure this does not happen, privacy must only be breached with the clear, explicit and prior written agreement of the participant who must be given a complete understanding of the need for the breach, along with the potential risks and benefits for doing so and must be limited to only absolute necessity to achieving an agreed research purpose. Personal health and genetic data must never be sold or provided for any purpose outside the agreed research.

However, this is becoming more problematic in the age of bio-banking, when consent is often very broad and covers future research. The "agreed" research is often not as narrow as most clinical trials and may be unknown at the time of initial consent.

### **8.8 Privacy, Security and Access on Aggregated Data**

In many analyses, HEOR data are subsequently anonymized and analyzed on the group level. Examples include the analysis of relative treatment effect in a clinical trial, the analysis of the frequency of adverse events in an observational study, or in assessing the general public's preferences for health outcomes. Unless the data are identifiable, e.g., Chronic Condition Data Warehouse (CCW)<sup>66</sup>, the arguments for keeping these data confidential are not very strong and may relate to the proprietary nature of the data or contractual agreements the researcher may have with a manufacturer or data provider.

## **APPENDIX 9            The Role of Institutional Review Boards (IRBs) and Independent Ethics Committees (IEC)**

### **9.1    Background**

Institutional Review Boards (IRBs) are also known as Independent Review Boards (IRBs) (US terms), independent ethics committees (IEC), clinical research ethics committees (ECs) (EU term), or research ethics committees (RECs) (UK term). The term IRB may be interpreted as IRB/IEC/REC for the remainder of this section.

All HEOR studies must be conducted according to ethical standards for healthcare research, regardless of whether the study is submitted to an IRB or not.

The IRB is an independent body (a review board or a committee that may be sub-institutional, institutional, regional, national, or supranational), constituted by medical professionals, biomedical scientists, those with other disciplinary expertise and 'lay' members, e.g., relevant member of the community, patients (or representatives) with interest in holding patients' interest to the highest standards. Ethical review of research proposals should include input from at least one lay person.

The IRB is a committee that has been formally designated to review, approve, and monitor biomedical and behavioural research involving humans.<sup>67</sup> IRBs often conduct some form of risk-benefit analysis in an attempt to determine whether or not research should be done.<sup>68</sup> IRBs are responsible for critical oversight functions for research conducted on human subjects, ensuring that they are 'scientific', 'ethical', and meet the relevant 'regulatory' requirements.

Although informed consent is often considered to be the cornerstone of research ethics, a prior requirement, i.e., that the research is judged to have adequate potential value to justify any risks to participants, is particularly important in recruiting healthy volunteers.

The legal status, composition, function, operations and regulatory requirements pertaining to IRBs may differ among countries, but should allow the IRB to act in agreement with GCP as described in ICH Topic E6 Guide for Good Clinical Practice (ICH-GCP).<sup>69</sup>

### **9.2    Typical Studies that will need IRB Approval**

ISPOR recommend studies involves following scenarios will need IRB approval:

1. Involves intervention to patients' standard of care.
2. The aim is to publish the study results in a medical journal. ISPOR suggest observing publication submission guidelines.
3. The study requires access to patients and physicians working within their confidential contracts, for example, data abstraction from patient notes.
4. A study conducted by academic institutions will go through institutional IRB review.
5. When IRB approval is required by the study sponsor for any other reason.



In order to minimize the impact of delays in starting clinical trials, IRBs are encouraged to form subcommittees that include patient representatives to address specific issues.

Equal opportunity should be given to qualitative and quantitative research projects. Research involving patients and patient organizations as investigators should be given weight along with other research presented. More importantly, researchers doing this type of research should be given direction and support from IRBs to ensure equal footing with other research projects. As a best practice, a sample set of questions/topics that are required to be part of any informed consent should be provided by researchers submitting to an IRB.

Both researchers and IRBs should make every effort to ensure that research proposals are not subject to duplicate reviews. For example, where it is mandated that a research proposal must be reviewed by a National Research Ethics Service (NRES) the researcher's university (or universities) ought not review the proposal. Similarly, for research that will be conducted by researchers employed by different institutions, a single institutional or sub-institutional REC should review the proposal.

### **9.3 Typical Studies that do not need IRB Approval**

ISPOR recommends that studies involving following scenarios will typically not need IRB approval,

1. Market research studies<sup>70 71</sup> and patient surveys focus on participants' opinion only. Researchers should observe relevant associations such as Market Research Association<sup>72</sup> for guidance. If a publication is planned, peer review journals would require prior IRB approval. Also academic institutions would require approval or determination of exemption.
2. Patient preference studies with no medical outcome as study measure.
3. Study based on literature review of secondary sources only.
4. Program evaluation, quality assurance, or quality improvement projects, which generally fall under the category of health care operations rather than research.
5. Studies that do not meet submission requirements from IRB. For example, UK HRA<sup>73</sup> classify research application as 'Research' if the answer to one or more of the following questions is YES:
  - i. Are the participants in your study randomised to different groups?
  - ii. Does your study protocol demand changing treatment/ patient care from accepted standards for any of the patients involved?
  - iii. Are your findings going to be generalisable?
  - iv. Will your study involve research participants identified from, or because of their past or present use of services (adult and children's healthcare within the NHS and adult social care), for which the UK health departments are responsible (including services provided under contract with the private or voluntary sectors), including participants recruited through these services as healthy controls?

## **APPENDIX 10            Considerations for Research Participant Involvement in Research Development and Design**

Consideration should be given to the involvement of research participants, including healthy volunteers, patients, protected class, children, and vulnerable populations. Members should endeavor to involve patients and their representatives as partners before, during, and after conducting research. Patient perspectives and those of patient representatives and advocacy organizations are especially useful to strengthen trial design and utility.

### **10.1 Healthy Volunteers**

Many clinical research studies need healthy volunteers as research participants because their health information can be used as a comparison to patient groups. Since healthy volunteers generally would not directly benefit from participation in a clinical trial, altruistic motivations and financial incentives rather than access to the latest treatment may be the main reasons for participation.

Researchers need to be particularly cautious in putting these volunteers at risk of harm for the good of others, and determine whether financial rewards for participation may lead some prospective volunteers – especially low-income individuals - to ignore various risks or conceal relevant health information<sup>74</sup>.

Any unnecessary risks should be minimized. Healthy research participants trust that researchers would not invite them to participate in research that would knowingly expose them to substantial risks of serious harm.

### **10.2 Patients**

As many patients are keen to gain access to the latest treatment, clinical research has the potential to exploit patient volunteers. This is particularly concerning for those who have inadequate access to available treatment, e.g., due to cost, and others with severe conditions who have not responded to standard treatment.

Researchers have a responsibility to clearly inform patient participants of the risk-benefit assessment of the research and to prevent any therapeutic misconception by distinguishing clinical trials from standard treatment and to ensure that they have the capacity to understand the particulars of the trials.

Researchers must not only implement solid preclinical research and study design safeguards, but also be diligent in ensuring that participants are not given unduly positive messages.

In clinical trials where there is no, or no effective, standard of care, and for life-threatening or serious and chronic conditions, combining and overlapping Phase 2 and 3 trials may be needed.

These patients do not have the luxury of time to wait for the traditional sequential approaches in the evaluation of efficacious treatments.

### **10.3 Protected Classes**

Currently, under U.S. federal regulations, IRBs must first determine that “the selection of subjects is equitable,” and is “particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons” (45 CFR 46.111(a)(3); 21 CFR 56.111(a)(3)). Moreover, IRBs must ensure that for these vulnerable populations additional safeguards are included in the study to protect the rights and welfare of these participants (45 CFR 46.111(b); 21 CFR 56.111(b)). Researchers should also check whether the federal departments they work with may have additional regulations that provide protection for specific groups. Similarly, EU GDPR-classified children, vulnerable populations and patients will need specific protection and explicit informed consent<sup>75</sup> as research participants.

### **10.4 Children**

Despite many advances, infants, young children and adolescents have not shared equally with adults in the achievements of biomedicine. Studies to develop therapeutics in children are necessary since some disorders affect only the young. Moreover, safety and effectiveness data gathered from adult populations may not apply to children. Research involving children is increasingly recognized as a moral imperative.

Nonetheless, researchers have additional ethical responsibilities toward children, who commonly lack mature decision-making capacity. Children are generally subject to the authority of adults and may defer in ways that can mask underlying dissent. To address such concerns, in addition to minimizing risk and maximizing the possibility of therapeutic benefit in clinical trials, parental permission and age-appropriate child assent to participate should both be sought.

### **10.5 Vulnerable Populations**

In addition to children, other population groups may be more vulnerable in research either because they have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity (e.g., dementia patients) or situational circumstances (as in the case of prisoners), or because they are especially at risk for exploitation (as in the case of persons who belong to undervalued groups in our society).

Members should ensure that special consideration is given to protect the rights and welfare of vulnerable individuals participating in HEOR. While members should avoid an overprotective attitude when assessing the vulnerability of research participants, it is essential to pay particular attention to designing a comprehensive informed consent and process, involving authorized substitute decision makers, assuring privacy and confidentiality protections, conducting benefit

versus risk assessments, preventing stigmatizing effects, and promoting equitable methods of subject selection.<sup>76</sup>

The CIOMS guidelines<sup>77</sup> provide specific guidance for research in low-income countries based on ethical concerns of possibility of exploitation. Because exclusion from research can result in or exacerbate health disparities, members should select research participants from groups or communities in such a way that the burdens and benefits of the research will be equitably distributed.

Before undertaking research in a population or community with limited resources, members should make every effort to work with the community to ensure that:

- The research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- Any knowledge generated will be made reasonably available for the benefit of that population or community.

The exclusion of groups or communities that might benefit from study participation must be justified. Groups that are unlikely to benefit from the knowledge to be gained in the research due to high prices of the drug/intervention or other infrastructure limitations, for example, must not bear a disproportionate share of the risks and burdens of research participation. Members should ensure that potential benefits and harms to research participants are reasonably balanced and risks are minimized.

## **10.6 Trial Participation**

The primary objective of almost all researchers in a Phase 3 clinical trial evaluating a promising treatment is to focus on the primary and secondary clinical endpoints for marketing authorization. Whenever feasible, the use of surrogate markers of disease progression should be considered and encouraged alongside trial data collection such as mortality. For example in HIV, CD4 count and viral load are validated surrogates that are able to guide treatment while avoiding untimely death among trial participants as study outcomes or data collection.

The use of a placebo arm in controlled trials in some circumstances, especially in life-threatening conditions, is controversial. In these cases, the use of a placebo is only permissible with a timely, crossover clinical trial design where the benefit/risk of doing so is clear, substantial and absolutely required.

In general, the use of a placebo arm where there is an accepted standard of care is not an option. In some countries, sponsors of a trial are responsible for the cost of the standard of care, used as part of trial design. In life-threatening diseases and conditions such as cancers where there is no effective standard of care, the study trial design should have a timely crossover arm, allowing patients in the trial to potentially benefit from the treatment arm.

## **10.7 Genetic Counseling**

When genetic counseling with family members is required, it is important to check the guidelines on how this should be approached. Furthermore, it will also be crucial to ensure that genetic information will not be used as a tool for discrimination in access to treatment.

### **10.8 After Trial Care**

The European Patient Federation reiterates that “healthcare must be based on the fundamental principles of equity and solidarity, and personalized medicine must not result in the exacerbation of health inequalities. Innovative treatments should be made available and affordable to all patients, not only those who can pay for them.

Patient access to the trial treatment at the end of the study period is then considered as a separate part of market access and reimbursement. This disconnect can leave trial patients without access to their treatment from the trial. It is highly recommended or a prerequisite that after trial completion where there is no effective standard of care, treatment is continued for patients who have responded well to the trial treatment until national or regional reimbursement negotiations are finalized.

This can be based on defined criteria with the treating specialist and perhaps for an agreed duration if needed. Historically, this was the model used when triple combination therapy for HIV was being trialed in Canada (LB, personal communications). This ensures that patients who participated in a trial will not be denied access to an effective treatment at the end of the trial period while market access and reimbursement negotiations are ongoing.

In an analysis of 30 drug assessments to the Canadian Agency for Drugs and Technologies in Health (CADTH), 119 patient insights were grouped into 3 tiers<sup>78</sup>:

Tier 1: Health status achieved or retained such as symptom relief, health-related quality of life using general or disease specific scales & slower disease progression;

Tier 2: Progress of recovery including fewer side effects, ease of adherence. In real world settings, the desired goals of prescribing, including adherence, that represent a shared decision making process involving personal treatment goals have recently been referred to as concordance<sup>79</sup>;

Tier 3: Sustainability of health including psychosocial quality of life such as mental, physical and emotional abilities, work, friends and family and independence from a caregiver.

Data and insights on progress of recovery and sustainability of health were very often not studied nor collected in clinical trials despite being closely aligned to patient needs. These 2 tiers are the basis for Patient Relevant or Important Information and recently have also been referred to as Patient Relevant Outcomes. Information on health status (Tier 1) were often determined by health care professionals focusing on clinical outcomes within a research paradigm. Also this information is often associated with Patient Reported Outcomes and used for label claims for investigational products.

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