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### *The ethics of informed consent in novel treatment including a gender perspective*

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#### Legal issues concerning informed consent in translational/clinical research and vaccination

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<sup>1</sup> **R** = Report, **DEM** = Demonstrator, prototype, **DEC** = Websites, press & media actions, videos, **OTHER** = Software, technical diagram, etc









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## Executive Summary

### Aims and scope

In the medical field, translational research objective is, first of all, to transfer scientific knowledge from laboratory and pre-clinical research to clinical research on human subjects and translate knowledge and advances generated in biomedical research into positive impacts on human health. Furthermore, translational/clinical research is the necessary step to move from clinical research to clinical practice, applying scientific findings to the routine healthcare that is daily provided (as a “two way road”, including the reverse path of transition from clinical practice to research).

The purpose of this report is to search for and verify if there are legal requirements concerning informed consent in translational/clinical research, with a special focus on vaccination, within the EU legal framework. Another essential aspect deals with checking the extent to which these standards are implemented in and harmonized through the six-selected countries considered in this task (Austria, France, Germany, Italy, Spain and the United Kingdom). Besides assessing the consistency of the legal framework, the focus will be on verifying whether or not gender and multicultural issues are taken into account by hard law and soft law.

### Methodology

The report adopts a narrative approach. After carrying out an analysis of the definition of translational research, legal issues are considered. Legal systems taken into account are the international one, the European one and six national laws of EU Member States (Austria, France, Germany, Italy, Spain and the United Kingdom). In addition, documents and opinions issued by national bioethics committees and research ethics committees in selected countries are also reviewed.

In this report, rules of conduct with no legal binding force are considered soft law (e.g. guidelines or recommendations). These rules are analysed together with institutional documents approved by national and international bioethics committees, which often contain non-binding opinions and recommendations. All legal instruments of positive law (laws, regulations and authoritative decisions, as well as case-law) are considered as hard law.

Concerning the study selection process, pairs of reviewers independently performed the search following the inclusion and exclusion criteria. For LUMSA, L. Nepi and L. Persampieri analysed national legal systems, while M. Daverio and V. Ferro explored international and EU legal systems. L. Palazzani, F. Macioce and A. Rinella proceeded to screen critically the proposed results and findings. In a subsequent phase, independent and external reviewers (L. d’Avack, C. Petrini, E. Rigo) have been asked to read a first draft of the report, so as to

highlight any lack of information, and to propose other or different data and resources. FISABIO carried out a literature review to assess if there is a commonly accepted definition of translational research in the scientific literature (J. Fons Martinez) and the analysis of the Spanish legal system.

Furthermore, international experts from academia, having considerable expertise in the field (also at the institutional level) were invited for internal workshops to acquire insights and opinions on the development of the report. These experts were selected within the six countries considered in the research protocol and the information gathered was taken into account, as reference for our review.

Findings were reported in the final draft by the members of the LUMSA research unit.

For further information, see annex 1 – Research Protocol.

## **Main findings**

First of all, the report attempts to provide a definition of translational research, pointing out that there is not a commonly accepted definition neither in literature, nor in regulations. Nevertheless, the idea that always appears behind each definition is the objective of "translating" knowledge and advances generated in biomedical research into positive impacts on human health (treatments, policies ...), overcoming existing obstacles in this process. Therefore, it is difficult to determine which legal requirements should be taken into account in this type of research, unless we consider as translational research each step from basic research to clinical practice and health decision making. Steps from a phase to another in clinical trials should equally be considered relevant. For this reason, the report also analyses regulations concerning innovative therapies, off-label use, compassionate use, observational studies and first-in-human clinical trials, to find analogies and differences between translational research and these kinds of research.

There is an increasing shift from the 'evidence-based' medicine model (e.g. which focuses on using randomized clinical trials to establish the best treatment for the average patient) to the 'personalized medicine' model or 'stratified/precision medicine' model (e.g., which considers differences among individual patients or homogeneous groups), even though they are both currently implemented in clinical practice. In the European legal systems, there is no specific regulation on translational research, but there are European and national regulations on the categories that translational research applies to, such as first-in-man clinical trials, observational studies, compassionate care and innovative treatments. The legal framework in this field is homogeneous.

The Clinical Trials Regulation (No. 536/2014) does not refer explicitly to translational research, but it implicitly promotes it. The regulatory analysis points out that obtaining informed



consent is necessary, both for interventional and non-interventional studies. Concerning clinical trials, which are interventional studies, the level of risk and its communication can change depending on the trial phase or the nature of the research. Thus, risk communication is of paramount importance in translational research and the informed consent process requires an even more careful and effective handling, due to the acceleration of research, to early access to innovative treatments, highly sensitive safety issues and the blurred boundaries between research and therapy.

Safety risk for participants is a central factor to consider from a legal point of view. There are some specific problems related to translational research “from bench to bedside”, as mentioned in the particular case of “first-in-man” or “first-in-human” trials. In this case, peculiar legal issues are strictly connected to the possible prevalence of the emphasis of research with human subjects on advancements in scientific knowledge over the protection of and the best interest of those who participate in the research; uncertainty, as preclinical research can fail to predict the risks for humans (it can predict clinical benefits that are not confirmed in humans, as well as risks that do not exist in humans); safety of research participants (benefits and risks should be carefully balanced, as the focus of research must always be placed on the patient’s interest); minimal risk (defining and respecting the threshold of “minimal risk” is a primary concern, especially when particularly vulnerable populations are involved).

Informed consent plays a central role, as people involved in a clinical trial have to understand that exploratory-experimental studies do not have a direct therapeutic objective and if volunteers misunderstand this, they may provide invalid informed consent. Effective strategies of risk communication (in terms of accuracy, clarity and understanding, tailored to different health literacy levels and cultural backgrounds) are key to ensuring human subjects’ full awareness of the extent of risk involved in a specific type of research (i.e. with regard to its nature and phase) and providing them with the necessary information to make a conscious decision with respect to the possible consequences of their enrolment, while overcoming misconception barriers linked to gaps at any stage of the informed consent process. Whenever new evidence arises, in any phase of research, with regard to specific risks for research participants, they should be immediately informed and reminded of their right to revoke consent without any negative consequences for them. Researchers have the duty to fully inform research participants about the nature and extent of increased risk for their health, in case they decide to stay in the research.

Clinical trials for experimental vaccines can be considered part of translational research, as an example of health research involving humans, with a special focus. Risk assessment in first-in-human trials for vaccines is specifically regulated by the EMA’s Committee for Medicinal Products for Human Use (CHMP). During decades of vaccine development and application, cases of severe damage caused by the products have been uncommon; in general, vaccines have an excellent safety record. Nonetheless, first-in-human clinical trials are a critical turning

point between preclinical studies and first human exposure and subsequent larger clinical trials in hundreds or (for many vaccines) thousands of subjects. For researchers, relevant risk assessment for first-in-human clinical studies means careful design and conduct of studies that reduce potential risk for humans.

With particular regard to vaccine trials, these fall within interventional research and healthy subjects are recruited. In this sense, there is a strong emphasis on safety and informed consent procedures.

Concerning validated vaccines and the topic of informed consent, consent can be formal, verbal or implicit. When mandatory vaccination is established in relevant provisions in law (Italy and France adopted hard law regulations in this sense), informed consent is nevertheless required.

As for the informed consent process, gender and cultural differences are not explicitly taken into account in the definition of legal requirements for the information provided and consent recording. Nevertheless, as a general principle, adequate and clear information must be given to the subjects involved, assessing that it has been understood. Thus, translation and cultural mediation may be used as means to fulfil those legal requirements and obtain a valid informed consent and this aspect is highlighted in guidelines and soft law.

## Tables of results

	International Soft Law	European Soft Law
Translational research	<p><b>World Medical Association (WMA)</b>, Declaration of Helsinki (1964, current version 2013) states that the goal of generating new scientific knowledge can never take precedence over the rights and interests of individual research subjects.</p> <p><b>WHO</b>, <i>World Report on Knowledge for Better Health</i> (2004)</p> <p>recommends that stronger emphasis should be placed on translating knowledge into actions (bridging the gap between what is known and what is actually being done).</p> <p><b>WHO</b>, <i>Guidelines for good clinical practice (GCP) for trials on pharmaceutical products</i> (1995) recalls the principles of the Declaration of Helsinki as far as non-therapeutic trials are concerned.</p> <p>National Institute of Health (NIH), <i>Biennial Report of the Director</i>, 2006-2007 offers a definition of translational research and its phases.</p> <p>UNESCO International Bioethics Committee (IBC), <i>Report on Social Responsibility and Health</i>, 2010, highlights that the gap between medical knowledge and medical</p>	<p><b>European Research Infrastructure in Medicine (EATRIS)</b>, <i>First-In-Man (FIM) Regulatory Manual</i> (2009), contains ethical and legal regulations about First-In-Man Trials.</p> <p><b>EGE</b>, <i>Statement on the Proposal for a Regulation of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human Use, and repealing Directive 2001/20/EC (COM 2012) 369 final</i> (2013)</p> <p>recommends independent multidisciplinary ethical evaluation of clinical trial proposals.</p> <p><b>EGE</b>, <i>The ethical implications of new health technologies and citizen participation</i> (2015)</p> <p>highlights the relevance of citizens engagement/participation in medical research in relation to new health technologies; different forms of citizen engagement in research are ethically analyzed; specific reference is made to expanded access and compassionate care.</p>

	<p>practice should be filled up.</p> <p><b>The Council of Europe, (Steering Committee on Bioethics)</b>, in the <i>Guide for Research Ethics Committee Members</i> (2010) stresses ethical issues related to biomedical research and in particular the connection between research and the community.</p> <p>CIOMS, <i>International Ethical Guidelines for Health-Related Research Involving Humans</i> (2016):</p> <p>translational research is one of the reasons for the revisions of CIOMS guidelines.</p>	
<b>Risk-proportionate informed consent</b>	No specific reference: it is the same as in clinical trials.	No specific reference.
<b>Validated vaccines</b>	<p><b>WHO</b>, <i>Global Vaccine Action Plan</i>, (2011-2020): six principle that can guide the GVAP (country ownership, shared responsibility and partnership, equity, integrity, sustainability, innovation) and that should be translated into different cultures.</p> <p><b>WHO</b>, <i>Considerations regarding consent in vaccinating children and adolescents between 6 and 17 years old</i> (2014) encourages to develop an informed consent procedure that is adapted to the local situation.</p>	<p><b>The European Centre for Disease Prevention and Control (ECDC)</b>, <i>Let's talk about prevention. Enhancing childhood vaccination uptake, Public Health Guidance</i>, (2016): the guide focuses on risk's communication.</p> <p><b>The European Centre for Disease Prevention and Control (ECDC)</b>, <i>Catalogue of interventions addressing Vaccine Hesitancy, Technical Report</i> (2017): the different kinds of interventions include a more effective communication of benefits and risks, to encourage vaccinations.</p>
<b>Clinical evaluation of vaccines</b>	<p><b>ICH</b>, <i>Good Clinical Practice</i> (E6) (1996, amended in 2016) describes informed consent as a process, documented in a written form.</p> <p><b>WHO</b>, <i>Guidelines on clinical</i></p>	<b>EMA</b> , <i>Guidelines on Strategies to Identify and Mitigate Risk for First-In-Human Clinical Trials with Investigational Medicinal Products</i> (2007, first revision 2017):

	<p><i>evaluation of vaccines: regulatory expectations</i> (2004) prescribes written informed consent, inclusion and exclusion criteria.</p> <p><b>WHO</b>, <i>Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO</i>, (2014): in the case of Ebola in West Africa, WHO states that it is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention (only in case of pandemics, and risk for public health).</p> <p><b>WHO</b>, Global Vaccine Action Plan (2011-2020). promotes the development of new vaccines.</p> <p><b>CIOMS</b>, <i>International Ethical Guidelines for Health-Related Research Involving Humans</i> (2016) concerning vaccines mainly focus on the topic of risk. There is no reference to the topic of informed consent.</p>	<p>regulations for the starting dose for a novel vaccine.</p>
<b>Meningitis</b>	<p><b>WHO</b>, <i>Position paper on Meningococcal Vaccine</i> (2015), emphasizes the importance of completing mass vaccination campaigns in the African meningitis belt.</p>	<p><b>EMA</b>, European Medicines Agency recommends approval of first vaccine for meningitis B, 2012: it recommends approval of first vaccine for Meningitis B.</p> <p><b>European Centre for Disease Prevention and Control</b>, <i>Expert opinion on the introduction of the meningococcal B (4CMenB) vaccine in the EU/EEA</i> (2017): the document is intended to support national decision-making in whether to introduce the vaccine in the national immunization programs.</p>

HPV	<b>WHO</b> , <i>Position paper on HPV Vaccine</i> (2017): it recommends that all countries proceed with nationwide introduction of HPV vaccination.	<b>ECDC</b> (European Centre for Disease Centre and Control), <i>Guidance for the introduction of HPV vaccine in European Countries</i> (2008): guidelines for the introduction of HPV vaccine in immunization programs of the European Countries.
RSV	There is no WHO position paper on RSV. <b>WHO</b> , <i>RSV Vaccine Research and Development Technology Roadmap</i> (2017): it contains priorities in implementing research on this vaccine.	<b>EMA</b> , <i>Guideline on the clinical evaluation of medicinal products, indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease</i> , 2017: guidelines for clinical development programs for medicinal products intended for the treatment of RSV.

	Translational research	Informed consent and risk communication	Pharmacovigilance for medicines for human use	Experimental vaccines	Vulnerability of clinical research participants
<b>EU hard law</b>	<p>There are no specific EU regulations regarding translational research.</p> <p>Regulation (EU) No. 536/2014 implicitly promotes Translational Research.</p>	<p>In non-interventional studies, the human subject's participation is informed and voluntary, but procedures are simplified. There is a lower risk than interventional clinical trials.</p> <p>In interventional studies, there are different levels of risk and contents of communication in relation to clinical trial phases (Regulation No. 536/2014).</p>	<p>Pharmacovigilance is considered as a non-interventional study.</p> <p>Rules governing pharmacovigilance for medicines for human use: Regulation (EU) no. 726/2004, as amended by regulation (EU) No. 1235/2010, and in the Directive 2001/83/EC, as amended by Directive 2001/84/EC; commission implementing regulation (EU) no. 520/2012; Good pharmacovigilance practices (GVP).</p>	<p>Vaccine trials are interventional studies.</p> <p>There are no specific European regulations concerning vaccine trials.</p> <p>Vaccination policy is a competence of national authorities. The European Commission supports EU countries to coordinate their policies.</p>	<p>Women during pregnancy or breastfeeding and children are considered patients with increased risk.</p> <p>Resolution of 14 February 2017 of the European Parliament (2016/2096 (INI)), calls on the Member States, applying Regulation (EU) No 536/2014, to guarantee an adequate representation of men and women in clinical trials.</p>

Country	Soft law on translational research	Informed consent and risk communication	Soft law on vaccine trials	Soft law on validated vaccines
<b>Austria</b>	There are no specific guidelines or recommendations regarding translational research.	The Austrian Bioethics Commission devotes significant attention to research on persons without the capacity to consent, with special consideration of the concept of risk. In the Opinion on <i>Research on persons without the capacity to consent-with special consideration of the concept of risk</i> (2013), it highlights the need to provide a clear definition of interventions with no or minimal risk and those with no or minimal burden; a list of no risk—no burden interventions is devised. However, there is no mention of different informed consent procedures tailored to the type of risk involved in clinical research/medical practice.	There are no specific guidelines regarding vaccine trials, as they fall under ethical standards regarding drug trials.	The Austrian Bioethics Commission places a strong focus on the ethical issues surrounding vaccination: The Opinion on <i>Vaccination-Ethical Aspects</i> (2015) stresses the fact that existing international surveillance programmes are still too heterogeneous and insufficient; the need for transparent and effective information to parents on access to no-cost vaccination schemes for children to avoid the phenomenon of vaccination refusal motivated by economic reasons. Information and scientific foundations pertaining to vaccines should be more strongly included in the training curricula of all health professions.
<b>France</b>	There are no specific guidelines or recommendations regarding translational research.	The French National Institute of Health and Medical Research (INSERM) recommends working closely with patient associations to include them in the expert appraisal process for clinical research projects on human subjects (e.g. patients associations should review the information leaflets and consent forms intended for volunteers invited to take part in these trials; this is meant to ensure that the information leaflet and consent forms are clear, accessible and complete.	There are no specific guidelines relating to vaccine trials.	The Report by Sandrine Hurel ( <i>Rapport sur la politique vaccinale, Janv. 2016</i> ) points out: the need for regular information and communication (web, social networks); the necessity of transparency and clarity of the messages and this implies a steering of the system where each of the actors of the vaccination policy finds his/her place.
<b>Germany</b>	The document on <i>In search of translational research. Report on the Development and</i>	There is no mention of different informed consent procedures tailored to the type of risk involved in translational/clinical	No guidelines are provided for experimental vaccines and the	<i>Recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute</i> (2017/2018) underline that it is



	<p><i>Current Understanding of a New Terminology in Medical Research and Practice</i> (2015), issued by the Institute of Research Information and Quality Assurance and the Berlin Institute of Health highlights that “the aim of translational research is to support an efficient translation “from bench to bedside” and “from bedside to bench”, hence from laboratory basic research into clinical therapies and vice versa”, underlining its intrinsic multidirectional nature; a clear conceptual framework is missing; the moral dimension of translational research focuses on the lack of implementation when translation fails to occur, resulting in a shortage of effective therapies.</p>	research/medical practice.	informed consent process, as they fall under the general indications regarding clinical trials.	<p>the physician’s responsibility to recommend the type and chronological order of vaccinations in each individual case, considering the indications and, where applicable, existing contraindications; as well as to inform patients of additional protective options;</p> <p>In case of injury, off-label use has consequences for liability and compensation and places particular obligations on the physician administering the vaccine regarding documentation and the provision of information.</p>
Italy	<p>There are no specific ethical guidelines or recommendations on translational research. Nevertheless, an explicit reference to translational research can be found in documents promoting initiatives, which focus on: knowledge transfer, fostering the implementation in clinical practice of research results, obtained both from state-funded research and the international scientific community</p>	<p>The Opinion on <i>single patient care and non-validated treatments, the so-called “compassionate use”</i> (2015) of the Italian National Bioethics Committee addresses the ethical issues of therapeutic treatments not validated by regulatory authorities, devoting attention to the analysis of the different aspects of the right to health, from freedom of care to informed consent, and the doctor-patient relationship.</p> <p>For patients who want to have access to a “compassionate” therapy there must be the guarantee of receiving complete</p>	<p>The Italian National Bioethics Committee in the Opinion on <i>Vaccinations</i> (1995 recalls that some vaccines are mainly or exclusively used in paediatric population; therefore, these subjects cannot be excluded from clinical research. However, the</p>	<p>The Motion on <i>the importance of immunization</i> (2015) of the Italian National Bioethics Committee strongly recommends to: implement effective advertising and information campaigns on mandatory and recommended vaccinations at national level, grounded in scientific evidence. Documents also highlight the necessity for family doctors and pediatricians to give adequate information to their patients on how vaccination is one of the most efficient treatments, with a very positive risk/benefit ratio.</p>

	(see the <i>Italian Ministry of Health National Programme for Health Research</i> , PNRS, 2017-2018).	explanations on the potential dangers of this type of treatment.	problem of involving participants unable to express a valid consent and directly protect their own rights, becomes particularly challenging in this context.	
United Kingdom	The goal of translational research is to target funding towards translational projects that require an interdisciplinary approach and a critical mass of researchers to get therapies to the point of clinical testing. However, there are no specific guidelines shedding light on the ethical issues stemming from translational research (see Medical Research Council, <i>MRC Strategic Plan 2014-2019. Research Changes Lives</i> ).	<p>Even if the risks of harm were within acceptable limits, and the participant had given valid consent to participate, the research may be in breach of the guidelines if it could have been carried out more safely (see General Medical Council, <i>Good Medical Practice</i>, 2013).</p> <p>The Report of the Nuffield Council on Bioethics on <i>Children and clinical research: ethical issues</i> (2015) stresses that innovative therapies outside the context of research are appropriate in cases of “compassionate use”. In these specific cases, health professionals have the duty to make sure that the information about the outcome of treatment and the clinical course of the patient’s condition is collected and made publicly available</p>	<p>Although guidelines have attempted to tackle the question of how much risk of serious harm a healthy volunteer can be exposed to, it is unclear what degree is acceptable, other than that the risk has to be very low (see Royal College of Physicians, <i>Guidelines on the practice of ethics committees in medical research involving human subjects</i>, 1996, 2007).</p> <p>The Briefing Note of the Nuffield Council on Bioethics on</p>	According to the Nuffield Council on Bioethics in the document <i>Public Health, Ethical Issues</i> (2007): vaccination policies that go further than simply providing information and encouragement to take up the vaccine may be justified if they help reduce harm to others, and/or protect children and other vulnerable people. The document concludes that there is not sufficient justification in the UK for moving beyond the current voluntary system for routine childhood vaccinations.

			<i>Zika: ethical considerations</i> (2016) focuses on the ethical problems surrounding the interactions between experimental vaccines and multicultural issues.	
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Country	Hard-law regulation on translational research	Informed consent and risk communication	"Compassionate use" and early access to innovative treatments	Hard-law regulation on vaccine trials	Mandatory vaccines for minors
Austria	There are no specific regulations regarding translational research.	Simplified procedures for non-interventional studies.	Permitted by the Drug Act (Arzneimittelgesetz) par. 8a in case of unauthorized medicinal products for human use, indicated for acquired immune deficiency syndrome, viral diseases, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions	There are no specific regulations regarding vaccine trials.	No
France	There are no specific regulations regarding translational research.	While requirements concerning consent differ according to the nature and level of risk, which is related to the research, the content of the information due to the subject is the same.	Permitted by art. L5121-12, Code de la Santé Publique, in case of treatment or prevention for serious or rare diseases, no proper treatment is available, efficiency and security are presumed according to the scientific knowledge.	There are no specific regulations regarding vaccine trials.	Yes (Loi n° 2017-1836)
Germany	There are no specific regulations regarding translational research.	For clinical trials on a person who is suffering from a disease which is to be treated by the investigational medicinal product, the duty to inform the patient is heightened to avoid therapeutic misconception	Permitted by the Drug Act (Arzneimittelgesetz), Chapter 4, Section 21.6, for administration to patients with a seriously debilitating disease or whose disease is life-threatening, and who cannot be	There are no specific regulations regarding vaccine trials.	No

			treated satisfactorily with an authorised medicinal product.		
Italy	There are no specific regulations regarding translational research.	Even if the risk is minimal, the Italian regulation concerning informed consent is the same.	Permitted by Law no. 648/1996, Law no. 94/1998, Decreto legislativo 219/2006, Law 57/2013, Law 79/2014, and two Ministerial Decrees of 2015 and 2017 for diseases with no therapeutic choice. Three types of medications can be included: innovative drugs authorized for sale abroad, but not in Italy; unauthorized drugs which underwent clinical trials; drugs to be used for a therapeutic indication different from those authorized (off-label use).	There are no specific regulations regarding vaccine trials.	Yes (Law 119/2017)
United Kingdom	There are no specific regulations regarding translational research.	The current UK legal framework allows a risk-related approach in obtaining informed consent, but informed consent must be always obtained in writing.	Permitted by Access to Medical Treatments (Innovation) Act 2016 if there is a good clinical evidence about effectiveness and safety of treatments. A public national database ensures the effective collection and dissemination of information about innovative treatments.	There are no specific regulations regarding vaccine trials.	No

## 1. First section – What do we mean when we talk about “translational research”?

To be able to specify the legal issues concerning informed consent in translational research the first step is to define properly the concept of “translational research”. Several articles try to discuss this concept, its models and phases.

### Objective and methodology

The objective of this section is to assess if there is a commonly accepted definition of “translational research” (TR) in the scientific literature.

Due to the existence of a systematic review done in this same field (the article entitled “*Mapping the evolving definitions of translational research*”, whose authors are Fort DG, Herr TM, Shaw PL, Gutzman KE and Starren JB) actual (published in 2017 by the *Journal of Clinical and Translational Science*) and practically with the same objective (“*Systematic review and analysis of definitions of translational research*”) (Fort et al., 2017), the methodology followed in this section is a narrative review using as corner stone the mentioned article and deepening in some of the most relevant articles of the field and other articles that were not included in that research.

The information is presented and structured by topics as follows:

1. Conceptual framework
2. Importance of Translational research
3. Different models to understand Translational Research
4. Phases/Blocks of Translational research
5. Conclusion
6. References

### 1.1 Conceptual framework

TR is a concept that has been subject of debate for more than 40 years, an example of this is the editorial published by the New England Journal of Medicine in 1974 entitled “*The Real Gap between Bench and Bedside*” (Wolf, 1974); even so Molas-Gallart, D’Este, Llopis and Rafols point to the origin of this concept in 1990s when the US National Cancer Institute developed the Specialized Programs of Research Excellence (SPOR), which promoted and facilitated the “translation” of basic discoveries into new interventions (Molas-Gallart et al., 2016). The importance of this topic has increased since the beginning of the XXI century and especially since 2008. (Fort et al., 2017; Keramaris et al, 2008; Drolet and Lorenzi, 2011).

The most repeated sentences used to define translational research are “*from bench to bedside*” or “*from bench to bedside and back again*”. Authors such as Marincola highlight the importance of understanding translational research as a bidirectional road “*Bench to Bedside*

*and Bedside to Bench*" (Marincola, 2003), so the observations of practitioners can also be tested in the laboratory. This two-way point of view is recognized in most TR models, but the majority of TR policy initiatives still consider it as unidirectional, focussing only in the first way ("bench to bedside"), and seeing it as consecutive gaps that have to be bridged (T1, T2...) (Molas-Gallart et al., 2016).

As Rubio et al. show in their article, the TR concept is not clearly defined and, to define it conceptually, it is important to review the definitions of the other types of research (basic and clinical research). The Members of the Evaluation Committee of the Association for Clinical Research Training used the following definitions: (2010)

- **Basic Research and Basic Science:** they highlight the characteristics of this kind of research that the director of the US Office of Scientific Development and Research mentioned in 1945, when he indicated that *"Basic research is performed without thought of practical ends. It results in general knowledge and an understanding of nature and its laws. This general knowledge provides the means of answering a large number of important practical problems, though it may not give a complete specific answer to any one of them."*
- **Clinical Research:** they propose the 3-part definition done by the National Institutes of Health (NIH) Director's Panel on Clinical Research in 1997:
  1. *"Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.*
  2. *Epidemiologic and behavioural studies.*
  3. *Outcomes research and health services research"*
- **Translational research:** They developed the following working definition: *"Translational research fosters the multidirectional integration of basic research, patient-oriented research, and population-based research, with the long-term aim of improving the health of the public"* (Rubio et al., 2010).

Sung et al. (2003) refer to the blocks or phases of TR as obstacles that impede efforts to apply science to improve human health in an expeditious manner. The obstacles that they identify include: lack of willing participants; regulatory burden; fragmented infrastructure; incompatible databases; lack of qualified investigators; career disincentives; practice limitations; high research costs and; lack of funding.

This concept of TR blocks as obstacles clearly shows the problem that TR tries to solve, that the research findings don't reach to a practical application in medical care and improve human health. Wagner and Srivastava show the lack of connection between science and clinical application and the function of TR connecting them when they say that *"translational research is a missing component between basic science and clinical application."* (Wagner et al., 2012)

Drolet and Lorenzi (2011) define translation as a process that *"describes the transformation of knowledge through successive fields of research from a basic science discovery to public health*

*impact*". And Fishbein, Ridenour, Stahl and Sussman (2016) explain that translational practices *"transform basic science discoveries into institutionalized practice and policy"*.

The variations in the definition of translational research are related to the differences in the models to understand it and in the definition of its phases or blocks and, as Fort et al. indicate, they reflect *"the changing nature and understanding of basic bioscience research and clinical medicine"* (Fort et al., 2017). The differences between the models and the phases are analysed with more depth in this deliverable.

Mollas-Gallart et al. highlight that TR represents different things for different stakeholders, saying that: *"for academics, TR represents (1) a channel to test whether novel ideas generated by basic science have the potential to translate into practical applications, (2) an opportunity to gain observational insights and develop novel scientific hypotheses to be tested in the lab, and (3) a means to gain legitimacy and improved access to research funding. However, for clinical practitioners such as physicians or clinical staff, TR is viewed primarily as responding to the need to shorten the path between scientific evidence and actual practice. Business organizations view TR as a process to accelerate the development of a new drug or therapy and as an opportunity to make go/no-go decisions at an early stage in the biomedical innovation process—potentially resulting in major savings by avoiding unproductive investments. Also, the fact that public organizations conduct TR is seen by industry as an opportunity to save on research whose returns are very uncertain."* (2016)

## 1.2 Importance of Translational Research

Woolf (2008) points out the lack of agreement in a unique definition of TR, but highlights that this kind of research is considered important, saying that TR *"means different things to different people, but it seems important to almost everyone."*

The importance that policy makers and the scientific community are giving to this type of research is clear if we analyse the increase of budget addressed to centres of TR, to research programs and activities of TR or the emergence of journals centred in this topic. (Drolet and Lorenzi, 2011; Woolf, 2008; Dougherty and Conway, 2008; Molas-Gallart et al., 2016). In USA, the NIH is especially active in this area, launching the Roadmap Initiative, Clinical and Translational Science Awards Program and the National Center of Advancing Translational Sciences; in Europe there have also appeared initiatives that promote TR and the relationship between basic scientist and healthcare professionals, such as the Networked Centres of Biomedical Research (CIBER) in Spain. (Molas-Gallart et al., 2016)

Fontanarosa and DeAngelis (2001) wrote an editorial in the JAMA, calling for papers on basic science and TR. They identified TR as the ultimate goal of medical research and indicated that its multidisciplinary nature offers medical research a virtually unlimited potential for discovery *"ranging from highly focused basic science findings that bridge important knowledge gaps*



*about fundamental mechanisms of disease to individually tailored preventive and therapeutic strategies”* (Fontanarosa and DeAngelis, 2001).

### 1.3 Different models to understand Translational Research

In this section are presented two different classifications of models to understand TR, on the one hand the differentiation made by Fort et al. between the “gap”, the “continuum” and the “mixed” model; and on the other hand the one made by Molas-Gallart et al between the “linear” and the “interactive-process” model of TR.

As stated before, Fort et al. (2017) identified 3 major “families” of definitions:

- **The “gap” model:** They locate their origin in the article written by Sung et al. in 2003 *“Central challenges facing the national clinical research enterprise”* (Sung et al. 2003); this model understands TR as the bridge gap between the end points of traditional basic and clinical research to overcome the obstacles to translate the knowledge generated into benefits for patients and / or the general population.
- **The “continuum” model:** With its origin in the article by Khoury et al. *“The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention?”* (2007). This new approach considers basic and clinical research as part of a same process in which phases are relatively continuous. In this model, as Fort et al said, scientific ideas are translated through a *“continuous research spectrum and phases in this continuum are labeled by common setting or research methods”* (Fort et al., 2017).
- **The “mixed” model:** It has its origin in the article *“The meaning of translational research and why it matters”* written by Woolf (2008). This model, composed by a practically hybrid group of definitions, has characteristics closer to the gap model (in the early structure) and to the continuum model (in the inclusion of later phases). Fort et al. (2017) also note that in this model clinical trial phases are generally not cited.

Fort et al. indicate that the TR definition has evolved from the “gap” model to the “continuum”, because they found that these definitions are more extended than the original ones (2017). Following this continuum model, Keramaris et al. highlight the importance of understanding medical research as a continuum where all branches of medical research are integrated and point out the cyclical nature of TR (2008).

Molas-Gallart et al. (2016) difference two approaches to the TR:

- **The linear model of TR:** This model understands the research as a linear progression of stages, which usually begins in the basic research and eventually turns into benefits for patients and/or general population. Some authors defend the bidirectional nature of TR, although the most common view focuses on a unidirectional way, from bench to bedside. This model identifies the main objective of TR as bridge the gaps to help the transfer of knowledge between the successive steps from basic research to its application faster; and the success of the translation of the new knowledge depends on the correct completion of each stage of the “translational continuum”. Under this model, the evaluation of the success of a TR programs is defined by the measure that has reduce or bridged the gaps and saved the time necessary to develop new treatments, practices or drugs.
- **The interactive-process model of TR:** This model focuses on the interaction and collaboration between the different stakeholders in the research (researchers, practitioners, patient communities, sponsors, medical institutions...). The model also contemplates that the medical research process doesn’t have to be always linear and recognises the existence of the “user-inspired basic research”. As Mollas Gallart et

al say *“instead of seeing TR as addressing the problems that appear at specific points in a traditional, staged, linear research system, in our approach, TR addresses the separation between different groups of researchers and stakeholders throughout the process, linking research to the development and application of solutions to health problems. To do so, TR focuses on processes—on how the sharing, exchange, and acquisition of knowledge are articulated and how different actors get involved in this process.”* (2016)

Other authors, such as Fishbein and Sung, highlight the importance of interaction and collaboration. Fishbein et al. (2016) give importance to the transdisciplinary collaboration, with interactions among people with different backgrounds; roles and perspectives within and through the phases of TR. Sung et al. (2003) highlight the need of a collaborative effort among the different stakeholders in order to eliminate the obstacles that impede the effective translation of knowledge.

## 1.4 Phases/Blocks of Translational research

Initially, Sung et al. (2003) identified two translational blocks or obstacles in translational research:

- Transfer discoveries from basic science to clinical studies.
- Translate new knowledge from clinical studies into medical practice and health decision making.

Later these two blocks were identified as T1 (from basic science to clinical studies) and T2 (from clinical studies into medical practice and health decision making). Wolf points out that most people have T1 in mind when they think about TR, and T1 is also the type of TR that usually gets the most funds; he criticises the distribution of funds (in 2002, NIH only spent 1.5% of its research budget on health services research) arguing on the one hand that in some diseases T2 can save more lives than T1 and, on the other hand, that investment in T2 is very important to salvage investment in T1 (Woolf, 2008).

The model of two blocks of translational research (T1-T2) evolved first into a model of three translational periods (the “3 T’s”: *“basic science translated to clinical efficacy (T1); efficacy translated to clinical effectiveness (T2); and finally effectiveness translated to health-care delivery (T3)”*) (Drolet and Lorenzi, 2011) and later towards models with more phases, such as the one proposed by Fort et al. with 5 phases (2017) or that of Fishbein et al. with 6 phases (Fishbein et al., 2016). The activities included in each phase and the scope of the TR have changed in each of these models. These changes in the number and characteristics of the phases also reflect the evolution of the types of research and the way of understand them.

For the purposes of this document, we focus on the model derived from the systematic review carried out by Fort et al. (2017), which included an analysis of similarity and consensus to identify an emerging consensus among the different definitions of the TR phases (figure 1). The result was a model that they proposed with 5 phases (T0-T4) that they summarized as follows: *“T1 involves processes that bring ideas from basic research through early testing in humans. T2 involves the establishment of effectiveness in humans and clinical guidelines. T3*

primarily focuses on implementation and dissemination research while T4 focuses on outcomes and effectiveness in populations. T0 involves research such as genome-wide association studies which wrap back around to basic research.”

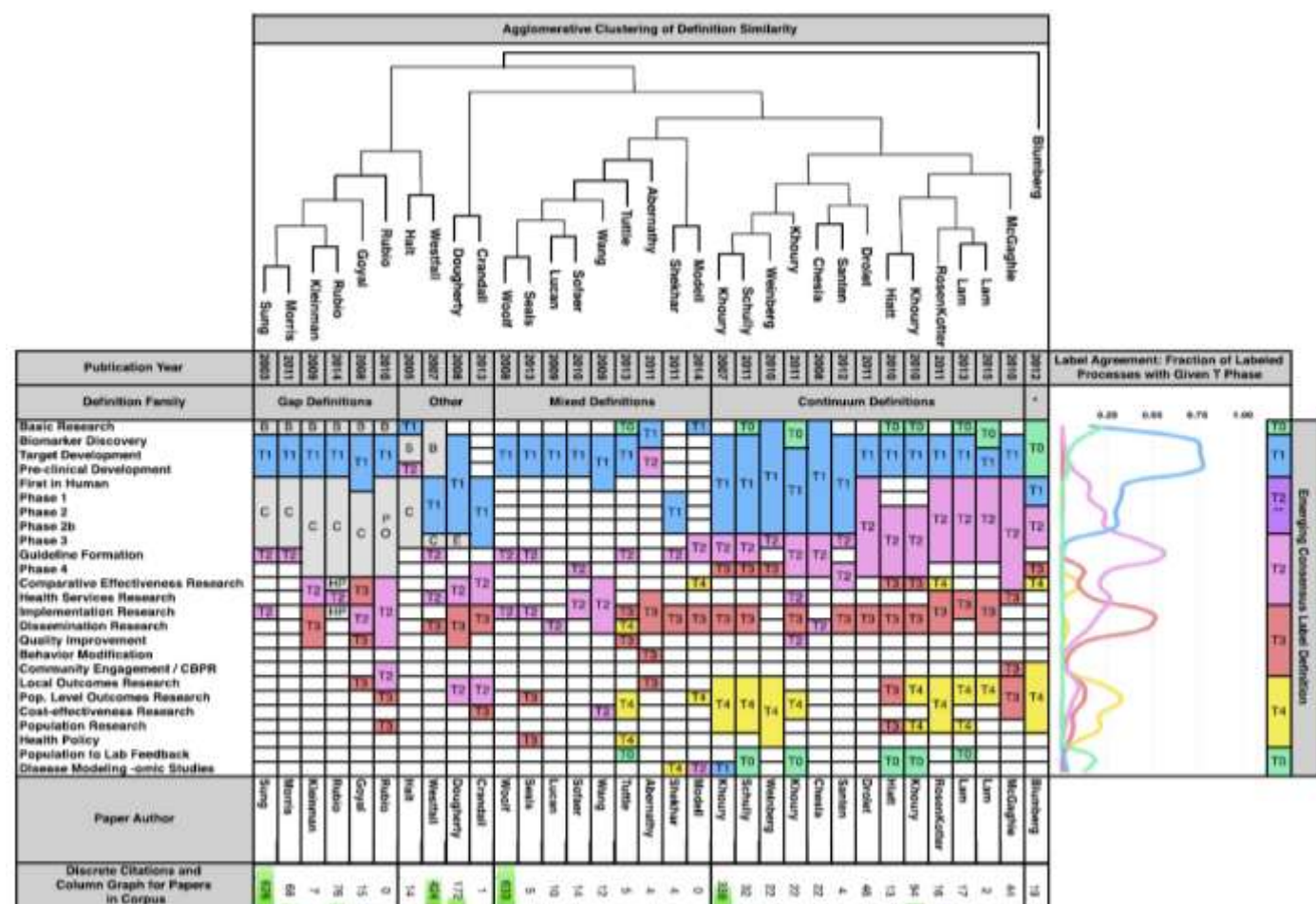


Fig. 1. Analysis of similarity and consensus<sup>3</sup>( Fort et al. 2017, 63)

## 1.5 Conclusion

TR is a topic that generates a lot of interest and its importance has been widely recognised; even so, it still not being a commonly accepted definition of “translational research” clearly defined. This fact highlights the need of a clearly defined and agreed model and definition of

<sup>3</sup> Notes done by Fort et al. to the figure: “Primary review results with consensus, clustering, and total citation information. The center of the figure shows the results of primary definition labeling. Blank cells indicate that the particular paper did not mention that research activity. Target development includes 3 named activities that were categorized the same by all papers (target validation, lead optimization, and lead development). The top of the figure shows a dendrogram representing the results of agglomerative clustering on the activity categories, resulting in 3 main definition families and a set of outliers (the “Other” grouping and Blumberg on the right), and also defines the order of papers for presentation. The far right side of the figure includes a consensus categorization and graph showing the frequency of assignment of each process to each T-phase as a fraction of all papers in the corpus. Early clinical trial phases are labeled as mixed T2\*\*. Although historic majority labeling is T1, since 2010 the predominant and emerging consensus label for these processes is T2. Citation counts for each paper are included below as a bar graph overlaid with the actual citation count for each paper.” (2017)

TR. Even so, the idea that always appears linked to the definition of TR is the objective of "translating" knowledge and advances generated in biomedical research into positive impacts on human health (treatments, policies ...), overcoming the obstacles that appear in this process.

Policy initiatives usually consider TR in a unidirectional way (from bench to bedside), but is important to consider it as a two-way road. Several authors point out the importance of the interaction and the collaboration between the different stakeholders involved and about the characteristics of multidisciplinary and transdisciplinary that this type of research has. It should also be borne in mind that TR represents different things for each stakeholder.

TR has evolved from a gap to a continuum model. The number of phases, blocks or steps, their definition and the activities that they include change from one model and author to another and, as Fort et al. suggest, it reflects "*the changing nature and understanding of basic bioscience research and clinical medicine*" (Fort et al., 2017).

Due to the lack of agreement with a clear definition of TR, it is difficult to determine the legal needs that should be taken into account in this type of research but, following the "continuum model" proposed by Fort et al., basic and clinical research should be considered as part of this same process of translational research.

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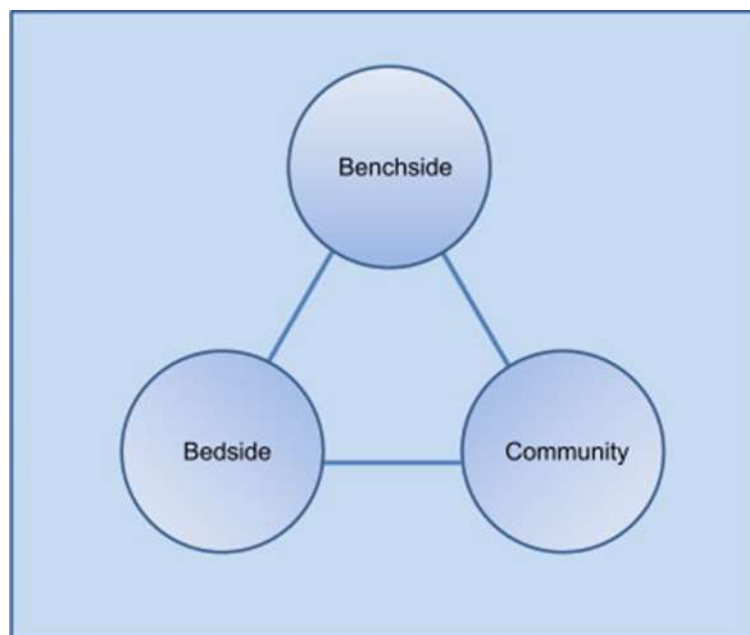
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## 2. Second section – Informed consent and translational research

### 2. 1 Translational research: bridging the gap between knowledge and health. A “two way road” and blurred boundaries between steps.

#### 2.1.1 Translational research as a “two way road”

In the medical field, translational research objective is, first of all, to transfer scientific knowledge from laboratory and pre-clinical research to clinical research on human subjects and translate knowledge and advances generated in biomedical research into positive impacts on human health (figure 2).



*Fig.2. EUSTM translational medicine model: the community as another key pillar (Cohrs et al. 2015, 88).*

It also entails the necessary steps to move from clinical research to medical practice and backwards (as a “two way road”, including the reverse path of transition from clinical practice to research), applying scientific findings to the routine healthcare.

#### 2.1.2 Ethical issues in translational research

##### 1. Safety, integrity, wellbeing of participants

The transfer from bench to bedside is the primary concern in translational research; nevertheless, researchers and physicians have a duty to protect the interests and welfare of

research participants/patients, making sure that the safety, integrity and wellbeing of individuals prevails over all other scientific advancements or commercial interests. There is a need to balance freedom of scientific research against respect for human dignity and human rights;

2. Risk/benefit proportionality (non-maleficence/beneficence); precaution when potential risks are higher than possible benefits.

Every research which aims at innovation entails uncertainties and risks, which may be unpredictable (totally or partially). Many risks related to translational research are common to the ones which are likely to be encountered in clinical research; but there may be some specificities stemming from the goal to foster a fast translation of research results into innovative strategies for the prevention, diagnosis and treatment of diseases: the “leap from bench to bedside”, peculiar to translational research, requires the duty to balance risks/benefits in a specific way. This expedited process needs greater precaution and caution to ensure that the timelines of procedures do not override the necessary protection and risk/benefit proportionality, which must be guaranteed to research participants. When risks are too high compared to the benefits than can be reached (non- proportionality of risks/benefits), there is a responsibility of researchers to stop research (even if requested by research participants/patients).

Hence, translational research may make the duty of safety for human subjects far more challenging, especially when moving from preclinical research to first-in-human trials: here safety issues are central, given that toxicity and adverse effects in humans may occur at very low doses or at doses that proved to be safe in animals. The degree of uncertainty in research and, notably at this initial stage of clinical research, cannot be easily overcome, since benefits or greater than minimal risks for participants deriving from a specific drug can only be discovered after testing it in trials. However, this can become particularly problematic when vulnerable population groups are enrolled in research (i.e. minors or fertile women). Even if many guidelines state that vulnerable individuals should be excluded from greater-than-minimal risk clinical trials, some documents stress the need to include them in research, so they can reap the benefits of their participation; therefore, despite the fact that vulnerable human subjects who are unable to consent should never be the first to take part in first-in-human trials, there may be trials where their participation is needed.

In translational research, risk is a central factor that has to be considered from an ethical point of view (see Petrini 2010). In addition to ethical problems common to every knowledge transfer process (for example identifying principles and values of the research, responsibilities of the various stakeholders, and an ethical oversight), there are some problems that are specific for translational research, “from bench to bedside”, as mentioned in the particular case of “first-in-man trials”. In sum, specific ethical issues related to first-in-man trials are:

- risk: in human research the emphasis on advancements in scientific knowledge might prevail over the protection and the best interest of those who participate in the research;



- uncertainty: first-in-man tests present uncertainties, as preclinical research can fail to predict the risks for humans; it can predict clinical benefits that are not confirmed in humans, as well as risks that do not exist in humans;
- safety of research participants: benefits and risks should be carefully balanced, as the focus of research must always be on the patient's interest;
- minimal risk: defining the threshold of "minimal risk" is of primary concern especially when vulnerable populations are involved.

### 3. Direct and indirect benefits

Scientific research may either have a potential direct benefit for the patient (for instance, the case of experimental treatments) or a potential indirect benefit deriving from the goal to obtain a general finding for medical research and subsequently for society or certain groups of persons.

In situations with no direct benefit, the assessment and consideration of risk is of special importance, notably when research undergoes an accelerated process, as in the context of translational research: all forms of research, which are not directly beneficial to the person concerned are usually only permissible if they bear no risk/burden or only minimal risk/burden.

This is all the more true when enrolling particularly vulnerable human participants, who require special protection by researchers, due to their specific health condition (i.e. pregnant women) or because they are unable to consent (i.e. minors). However, precautions towards vulnerable populations, which are necessary in many respects, might also significantly restrict the range of research options for the benefit of the groups of persons concerned and consequently deprive them of adequate opportunities stemming from medical progress.

### 4. Patient-physician relationship

Another specific aspect of translational research concerns the fact that, unlike clinical research, it stresses the connection between research and medical practice, highlighting the importance, from an ethical point of view, of strengthening the doctor-patient relationship, in order to facilitate the patient's understanding of the differences between what is therapy and what is research and the existence of possible "nuanced boundaries" between the two.

### 5. Justice: fair access and non-discrimination

It is necessary to carry out a fair patient selection, which avoids unacceptable levels of risk, excluding forms of exploitation of healthy volunteers (or other participants), through undue inducement or compensation.

### 6. Integrity of research

Acceleration in translating research results in medical practice does not mean disregarding the scientific soundness of findings and the reliability of the methods of analysis used to



obtain such findings; therefore, all forms of research misconduct should be avoided, including conflicts of interests involving sponsors and those who administer experimental treatments (i.e. no pressure must be exerted by physicians and researchers, for professional reasons, on emotionally vulnerable individuals affected by severe, rare or life-threatening diseases).

7. Protection of confidentiality of identifiable medical data (especially when it is used in different research studies or transferred from medical practice to research).

8. Necessity of an adequate ethical oversight

Devising new ways to face the challenges of translational research through an adequate ethical oversight (providing for the participation of many experts, according to the type of research, in ethics committees) at the laboratory or preclinical research level is equally crucial, so as to be able to come up with rigorous safety criteria in making the decision to start first-in-human clinical trials and to guarantee that the acceleration of processes does not result in overlooking pivotal ethical issues.

In summary: alongside the undeniable opportunities linked to fostering the translation of laboratory findings into novel preventive, diagnostic and therapeutic options, translational research equally raises many ethical concerns with regard to guaranteeing an adequate protection of research participants, through appropriate safety assessments, in ways that avoid jeopardizing participants' health, especially in first in human clinical trials.

### 2.1.3 Informed consent in translational research

In this context, informed consent plays a central and specific role.

People involved in a translational/clinical trial have to understand the exploratory nature of the study: namely, the fact that it does not have a direct therapeutic objective and that it entails risks, potential and possible direct or indirect benefits. If volunteers misunderstand this, they provide invalid informed consent.

Effective strategies of risk communication (in terms of accuracy, clarity and understandability, tailored to different health literacy levels, age/gender and cultural backgrounds) are key to ensuring human subjects' full and critical awareness of the extent of risk involved in a specific type of research (i.e. with regard to its nature and specific phase) and providing them with the necessary information to make a conscious decision in participating to the study with respect to the possible consequences of their enrolment, while overcoming misconception barriers linked to gaps at any stage of the informed consent process.

Respecting the autonomy of participants in translational research requires an even more careful and effective handling of the informed consent process, by envisaging a differentiated approach to information, adapted to the benefits and risks related to the specific research study and research phase provided before, during and after the study.

Fostering communication strategies to improve the physician-patient relationship is essential in this context (notably in moving backwards from “bedside to the bench”), in order to ensure the “circularity of information” (not only from the physician to the patient, but also from the patient to the physician) and increase health benefits for the community as a whole: for instance, improving patient communication of possible adverse events related to experimental or validated drugs, also after the end of a research study or a medical treatment.

Whenever new evidence arises, in any phase of research, with regard to specific risks for research participants, they should be immediately informed and reminded of their right to revoke consent without any negative consequences in terms of cure and care for them. Researchers have the duty to fully inform research participants about the nature and extent of increased risk for their health, in case they decide to stay/remain in the research. Researcher should assure freedom for research participants to withdraw from it at any time, without any negative consequences.

#### 2.1.4 Analogies and differences between innovative therapies and translational research

There is an increasing shift from the ‘evidence-based’ medicine model (e.g. which focuses on using randomized clinical trials to establish the best treatment for the average patient) to the ‘personalized medicine’ model or ‘stratified/precision medicine’ model (e.g., which considers differences among individual patients or homogeneous groups), even though they are both currently implemented in clinical practice.

Concerning personalized medicine, innovative therapies (see hard law and soft law below) can be placed in the context of blurred boundaries between research and treatment, which is a common element that these therapies share with translational research.

Innovative therapies coincide with different categories, one of which may fall under translational research:

##### *Off-label treatment*

It refers to “the use of treatments which differ from those authorised, with a scientific basis of efficacy and tolerability”. In this sense, it is not far from traditional standards of experimentation and use of drugs, “but allows, exceptionally, under medical control, the use of treatments not yet validated by healthcare regulatory authorities in cases where patients have a serious pathology without validated therapies or with validated therapies which are not effective” (The European Group on Ethics in Science and New Technologies, EGE, 2015).

Despite this commonality, a number of differences can equally be devised between innovative therapies and translational research, when considering the category of the so-called ‘compassionate use’ of drugs:

- in this case, an innovative therapy is “a newly introduced or modified therapy with unproven effects. Unlike research, which follows a predetermined course of action set out in a protocol, experimental or innovative therapy involves a more speculative approach to the patient’s care and may be adapted to the individual’s response” (UK Nuffield Council on Bioethics, 2016).
- non-validated treatments are usually used as a well-motivated and strictly monitored exception, in front of a life-threatening situation or a particularly severe disease and when there are no recognised effective alternatives in terms of treatments.
- non-validated treatments are for personal and non-repetitive use (e.g., it involves the use of individual or group treatments).
- such compassionate use drugs must have a reasonable scientific basis (i.e. data published in international scientific journals, results on animals and preferably results from phase I clinical trials).
- the prescription requires an adequate assessment by a panel of experts, under full transparency conditions, without conflicts of interest, ensuring publication of the products’ composition and the treatment’s results, along with a detailed explanation to the patients of the potential dangers, and possible lack of benefits, as well as the drugs’ risks and costs.

Translational research does not concern exceptional situations involving a single research participant or patient, without validated treatments as an alternative, but clinical trials with cohorts of volunteers, in order to seek and test better therapeutic opportunities.

Innovative therapies may raise a set of ethical problems deriving from the blurred distinction between research and treatment:

- researchers and physicians involved in innovative therapies should focus on fostering the doctor-patient relationship and avoiding putting it at risk because of possible conflicts between ensuring developments in the medical field and protecting the welfare of patients, since patients may perceive their role as being instrumentalised for experimental or professional goals; it may also occur that patients welcome enthusiastically the possibility to start experimental treatments, while overlooking the risks, as they consider these therapies as a “last resort” option/hope to get better;
- the patient’s ability to express an actual informed consent may be undermined by his/her emotional condition related to being affected by an incurable and life-threatening disease;
- understanding whether there is a duty for health professionals involved in innovative therapies to share the information regarding positive and negative results of interventions (e.g. this data may be useful for other patients, who could be informed about evidence-based benefits and risks, or to improve future research programs) may become problematic, as well as envisaging ways to implement this duty;
- equal access to innovative therapies might be another problem (e.g. only those patients that voluntarily seek or have access to sources of information on these experimental treatments are likely to rely on these therapies)
- health professionals may be put under pressure, because patients constantly request these experimental treatments, after having collected information on their own.

## 2.2 Translational research: international recommendations and guidelines

In the International and European soft law, there are no specific regulations regarding translational medicine (with the only exception of CIOMS).

CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans* (2016)

One of the reasons of the revision of CIOMS guidelines is the heightened emphasis, since 2002, on translational research, implementing relations between basic research advances and their use, in order to develop new therapies or medical procedures (see CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, Preface).

Particularly significant for translational research are:

- Guideline 4, *Potential individual benefits and risks of research*: the Guideline offers criteria to balance and assess benefits and risks for participants. This is a central aspect for translational research because translational research has the aim to gain new scientific knowledge, ensuring at the same time research participants' safety. The Guideline recommends that potential individual benefits and risks of research must be evaluated in a two-step process. First, the potential individual benefits and risks of research must be evaluated and second, the aggregate risks and potential individual benefits of the entire study must be assessed and considered appropriated. For research that includes potential individual benefits for the participants, risks are acceptable if they are minimized and outweighed in consideration of the potential benefits for the participants; for research interventions or procedures that offer no potential individual benefits to participants, the risks must be minimized and appropriate in relation to the social and scientific value of the knowledge to be gained (expected benefits to society from the generalizable knowledge). The aggregate risks of all research interventions or procedures in a study must be considered appropriate in light of the potential individual benefits to participants and the scientific social value of the research. The Guidelines underline that the assessment of minimal risk must include cultural factors because different conditions can alter the possibility of risk for people involved in the research (see Commentary on Guideline 4). Research ethics committees must be careful in this assessment to avoid that participants or groups of participants be exposed to greater risks in research merely because they are poor, members of disadvantaged groups or because their environment exposes them to greater risks in their daily lives.
- Guideline 5, *Choice of control in clinical trials*. Translational research involves patients in testing new therapies or drugs and for this reason a control group is needed; this is why this Guideline is relevant for translational research. As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of diagnostic, therapeutic, or preventive intervention receive an established effective intervention. Placebo may be used as a comparator when there are compelling scientific reasons for using it (this is when a trial cannot distinguish an effective intervention from an ineffective one without using placebo) and when delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimised.
- Guideline 6, *Caring for participants' health needs*: this part regards translational research as it underlines that care for research participants must be adequately addressed by researchers and sponsors. Researchers and sponsors must show care and concern for the health and welfare of study participants because research with humans often involves interactions that enable researchers to detect or diagnose health problems during recruitment and the conduct of research; furthermore, clinical research often involves care and preventive measures in addition to the experimental interventions. In some cases, participants may continue to need the care or prevention provided during the research after their participation in the study has ended. This may include access to an investigational intervention that has demonstrated significant benefit. The Guideline recommends to include in the informed consent process the information on care for participants' health need, during and after the research.
- Guideline 7, *Community Engagement*: this Guideline concerns translational research, as translational research includes the role of the community. The Guideline recommends that there should be community engagement in the design, development, implementation of the informed consent process

(Guideline 7, *Community engagement*), in order to ensure that documents for informed consent are understandable and appropriate for potential participants to the research; the Guideline underlines that the community must not be permitted to insist on including or omitting certain procedures that could threaten the scientific validity of the research; at the same time, the research team must be sensitive to cultural norms of communities, in order to support collaborative partnerships (see Commentary on Guideline 7).

WHO, *World Report on Knowledge for Better Health* (2004)

The document contains references to translational research, considered as a process linking scientific knowledge to health care and in particular to public health. Translational research is defined as “the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease”. Chapter 1 (“Learning to improve health”) and chapter 4 (“Linking research to action”) are important for a general orientation about translational research.

The document specifically underlines that:

- the culture and practice of health research should go beyond academic institutions and laboratories to involve health service providers, policymakers, the public and civil society;
- in order to respond more effectively at the national and global level to today’s public health challenges, health research must be reoriented to strengthen health systems by translating knowledge into action to improve public health, besides attracting more investments for more innovative research on health systems;
- research is essential, but not sufficient, to decide which policies and practices to promote and implement. The notion of “knowledge for better health” involves a continuous cycle of research, application and evaluation, and learning from that experience.

In chapter 5 (“Recommendations and actions”) it recommends that:

- stronger emphasis should be placed on translating knowledge into actions to improve health thereby bridging the gap between what is known and what is actually being done;
- as research should inform practice, practice should equally inform research; one of the key contributions of research to health systems is the translation of knowledge into actions: to use research to shape health policies, health practices and public opinion;
- countries should invest in building national capacity for the ethical review of health research;
- international agencies should consider establishing an international code of conduct for equitable partnerships in health research.

UNESCO International Bioethics Committee (IBC), *Report on Social Responsibility and Health*, 2010,

From the perspective of Global Health Care, IBC highlights that “there is a growing gap between medical knowledge and medical practice, sometimes referred to as ‘know-do gap’. Millions of people have no access to proper health care. Even in developed countries, many well established preventive treatments are not used, resulting in complications and sometimes the need to use more expensive treatments when the preventable illness actually occurs. Many effective treatments are frequently underused or misused”.

As mentioned above, improving health requires the application of research, namely of biomedical sciences: in the "know-do" gap, there is the space of translational research, trying to join research and clinics and needing ethics guidelines for this scope.

National Institute of Health (NIH), *Biennial Report of the Director*, 2006-2007

In this document clinical and translational research are considered together, because the two areas overlap, with translational efforts often focusing on overcoming barriers that impede the progress of clinical research. NIH offers the following definition: "Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community" (NIH, *Definitions under Subsection 1-Research Objectives, Institutional Clinical and Translational Science Award*, 2007). It has to be recalled here that cost-effectiveness of prevention and treatment strategies is also an important part of translational science.

Following this definition, NIH considers translational research as divided in two stages:

- Applying discoveries generated during research in the laboratory to the development of studies in humans. Such preclinical translational investigations are often carried out using animal models, cell cultures, samples of human or animal cells, or experimental systems.
- Taking results from studies in humans and applying them to research on enhancing the adoption of best practices in the community.

Furthermore, in the Translational Science Spectrum (April 2015), NIH includes each stage of research along the path from the biological basis of health and disease to interventions that improve the health of individuals and the public. In NIH's perspective, the distinction is between different phases, i.e. basic research, pre-clinical research, clinical research, clinical implementation and public health. Basic research scientists provide clinicians with new tools that can be used for patients, and clinical researchers make new observations about the nature and progression of disease that often stimulate basic investigations. Research on new outreach approaches and the *cost-effectiveness* and *real world* feasibility of prevention and treatment strategies are important aspects of this endeavor, as they provide the feedback necessary to ensure the practicality of interventions. Translational research goes beyond clinical research, implementing the relation between research and health, including public health, as mentioned above.

The European Science Foundation (ESF), *Implementation of Medical Research in Clinical Practice*, 2011

This document explicitly deals with translational research and particularly with the difficulty to set clear boundaries between basic research and clinical research.

In this regard, it states that: “clinical research can be looked upon as a broad term that includes basic-oriented research, disease-oriented research with animal models, i.e. translational research, patient-oriented research and outcome research. The terminology is varied across Europe and the rest of the world, but in spite of this it is important to stress that all aspects of biomedical research are necessary. Basic oriented research aims to generate knowledge but may perhaps not be immediately relevant for practical applications in patient care. Clinical research is described by others only as research protocols involving patients. For everyone involved in this research area the important thing is that the whole spectrum of research is essential, from basic, through translational to patient-oriented research and back again. One part is ineffective without the other” (European Science Foundation 2011, 5)

In addition, in Annex 2(Glossary), it defines translational research as “the conversion of basic research advances into products that can be tested on humans”.European Research Infrastructure in Medicine (EATRIS), *First-In-Man (FIM) Regulatory Manual* (2009)

The document contains regulations concerning First-In-Man trials, according to International and European guidelines. In Europe, EATRIS one of the most important initiatives in order to promote translational research is the, encouraged by the European Commission. EATRIS is a pan-European infrastructure whose main objective is to facilitate the translation of research findings into innovative products for the prevention, diagnosis and treatment of diseases of particular public health significance and economic impact.

European Group on Ethics in Science and New Technologies (EGE), *Statement on Gene Editing*, 2016

This document, in addressing the ethically problematic issues surrounding gene editing, points out how challenging it can be to provide a clear distinction between basic and translational research.

In the context of germline gene modification, the EGE notably stresses that: “It has been suggested that research with a clinical application, as distinct from basic research, should be subject to a moratorium. We would be cautious in terms of whether such a clear-cut distinction can be made between basic and translational research. Likewise, the blurring of the lines between clinical applications in pursuit of therapeutic or enhancement goals (albeit the ethical issues pertaining to each may be different), must be considered”. Moreover, in another part of the statement, the European Group underlines once again that “because of the blurring lines between basic and applied research, some also call for a moratorium on any basic research involving human germline gene modification until the regulatory framework is adjusted to the new possibilities”.

## 2.2.1 The primary duty of safety for research participants in the leap from bench to bedside

First-in man (or “first-in-human”) trials – trials with no specific therapeutic objective - are one of the principal means of translational research and are regulated by soft law orientations.

World Medical Association (WMA), Declaration of Helsinki (1964, current version 2013)

The protection of clinical trial subjects is consistent with the principles set out in the Declaration of Helsinki. In the Declaration, there is no explicit reference to translational research. Concerning related issues, as for the general duty to protect the subjects who take part in medical research (see the Declaration, in particular Articles 4, 6 and 7) and implement measures to minimize risk (see articles 16-18), the Declaration states:

- 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 subjects (see article 8);
- research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional (see article 12);
- physicians who combine medical research with medical care should involve their patients in research, only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects (see article 14).

All vulnerable groups and individuals must be protected with special consideration; medical research with vulnerable groups is only justified if the research is responsive to the health need or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, the group should stand to benefit from the knowledge, practices or interventions that result from the research (see articles 19 and 20).

Article 26 of the Declaration states the principle of informed consent, including the right of the subject to withdraw consent at any time without reprisal.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines.

ICH Guidelines contain references to research involving human, in particular:

- Pharmacovigilance (E2A-E2F) (1994);
- Good Clinical Practice (E6) (1996, amended in 2016);
- General Considerations on Clinical Trials (E8) (1997);
- Choice of Control Group in Clinical Trials (E10) (2000);
- Clinical Trials in Paediatric Population (E11-E11A) (2000).

Guideline E6 describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and Ethics Committee/Independent Review Boards. In ICH guidance, there are references to informed consent, but referred to clinical trials in general (informed consent is required and it is a



process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate; IC can be oral or written, and it must be documented).

WHO, *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products* (1995)

There is no specific reference to translational research, but by providing a basis both for the scientific and ethical integrity of research involving human subjects, the Guidelines recommend the protection of the rights and safety of subjects, including patients, and that the investigations be directed to the advancement of public health objectives. The Guidelines also recall that the investigator must take appropriate measures to ensure the safety of clinical trial subjects.

In Annex 1, referring to the Declaration of Helsinki, the Guidelines encompass orientations for non-therapeutic biomedical research involving human subjects, recalling that:

- in the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
- the subjects should be volunteers--either healthy persons or patients for whom the experimental designed is not related to the patient's illness.
- the investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
- in research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

EMA, *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*, 2007 and its first revision (July 2017).

A specific reference on this topic is the EMA *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*, 2007 and its first revision (July 2017). The revision is intended to further assist stakeholders in the transition from non-clinical to early clinical development and in identifying factors influencing risk for new investigational medicinal products.

In the document, strategies for mitigating and managing risks are envisaged, including principles on the calculation of the starting dose to be used in humans, the subsequent dose escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts.

The Guideline:

- recommends that the safety and well-being of trial subjects (be they patients or healthy volunteers) should always be the priority and special consideration should be given to characterising risk and putting in place appropriate strategies to minimise risk;

- aims to address as far as possible the important issues that may need consideration during the process of designing a set of studies in a clinical development programme, such as quality aspects, nonclinical aspects, dosing selection.

The early clinical development of human medicinal products has an intrinsic element of uncertainty in relation to both the possible benefits and risks of a novel drug candidate. Uncertainty may arise from particular knowledge, or lack thereof, regarding the mode of action of the Investigational Medical Product, the presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies. In addition, risks may derive from the characteristics of the population to be studied, whether healthy volunteers or patients, including potential genetic and phenotypic polymorphisms influencing Pharmacodynamics and Pharmacokinetics. For these reasons, careful dosing selection of an Investigational Medical Product is a vital element to safeguard the subjects participating in First-In-Human and early Clinical Trials. Special attention should be given to the estimation of the exposure to be reached, at the initial dose to be used in humans, and to subsequent dose escalations to a predefined maximum expected exposure. The expected exposure in humans at a dose to be given, in comparison to the exposure at which certain effects were observed in animals or earlier in the study in humans, is considered more relevant than the relative dose levels between animals and humans.

In order to further limit the potential for adverse reactions in humans, safety factors are generally applied in the calculation of the starting dose in humans. In healthy subjects, safety factors should take into account potential risks related to: the novelty of the active substance; its pharmacodynamics, including irreversible or long lasting findings and the shape of the dose-response curve; the relevance of the animal models used for safety testing; the characteristics of the safety findings; uncertainties related to the estimation of the MABEL (minimal-anticipated-biological-effect level), PAD (Pharmacologically active dose) and the expected exposure in humans. Similar considerations apply for the identification of a safe starting dose in patients. The goal of selecting the starting dose for First In Human/early Clinical Trials in patients, i.e. where there are no previous data in healthy volunteers, is to identify a dose that is expected to have a minimal pharmacological effect and is safe to use. The starting dose should also take into account the nature of disease under investigation and its severity in the patient population included in the Clinical Trials.

In addition, EMA recommends that

- trials should be designed in a way that optimises the knowledge to be gained from the study without exposing excessive numbers of subjects while ensuring the safety of participants;
- the overall study design should justify the inclusion of each study part considering the data each will provide and the time available for integrated assessment;
- safety should not be compromised in the interests of speed of acquiring data or for logistical reasons;
- risk mitigation activities should be proportionate to the degree of uncertainty and the potential risks identified.

The choice of subjects (healthy volunteers as well as patients), among other ranges, includes a patient's ability to benefit from other products or interventions, the predicted therapeutic window of the Investigational Medical Product, and factors relating to special populations, including age, gender, ethnicity and genotype(s).

There is no explicit reference to the topic of informed consent in first-in-human clinical trials. But some indications may be implicitly deduced.

Besides risk in first-in-man trials, there are some others references, related to clinical trials in general, that can be useful orientations regarding the protection of those who take part in the research.

The Council of Europe, (Steering Committee on Bioethics), *Guide for Research Ethics Committee Members* (2010)

Although it does not refers explicitly to translational research or first-in-human trials, the document is an important reference regarding ethical issues related to biomedical research and in particular the connection between research and the community, as we briefly recall here:

- research involving humans must justify the proposal to conduct the research in human beings and this not only as far as the research has the aim of improving people's health but also showing that similar results cannot reasonably be obtained by other means, for example by mathematical modelling or research in animals;
- researchers who plan to recruit healthy volunteers must abide by the general ethical principles pertaining to biomedical research;
- the Research Ethics Committee must be satisfied that the research will entail no more than acceptable risk and acceptable burden for those participants. For safety reasons, it is advisable to restrict the number of participations for each individual volunteer;
- for any biomedical research involving human beings, the researchers must ensure that the risks and burdens of research participation are not disproportionate to any potential benefits. Risks and burden should always be minimised;
- biomedical research involving interventions must not be allowed to proceed unless the potential research participant has given his or her consent. Consent must be informed, and freely given (requirements that stem from the ethical principle of autonomy).

EGE, *Statement on the Proposal for a Regulation of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human Use, and repealing Directive 2001/20/EC (COM 2012) 369 final* (2013)

In the document there are no explicit reference to translational research, but it recommends independent multidisciplinary ethical evaluation of clinical trial proposal, in order to safeguard the interest of clinical trials involving vulnerable groups, children, incapacitated persons, patients with mental illness, and research in emergency situations.

We can notice here that in the perspective of translational medicine, linking biomedical research to clinical trials, the relation between a researcher (one or more) and the patient gets more and more importance so that it could be needed further development on it.

EGE, *The ethical implications of new health technologies and citizen participation* (2015)

Special attention should be given also to the new forms of engagement of the community and of citizen in science and in biomedical research. Referring to the increasing direct involvement of citizens in science and medicine due to the emerging use of technologies in personal health, EGE recommends that care should be taken when using terms such as citizen “engagement”, “involvement” and “participation”. First, because such labels may function as a form of branding for activities or endeavors where alternative interests (such as financial, for example) dominate; second, because an overriding focus on empowering potential of engagement (while certainly warranting investigation) can draw attention from the double-edged nature of citizen involvement, which carries risks of exploitation, manipulation and control.

Regarding experimental care and therapies, in the EGE document are explained the characteristics of some phenomena that are blurring phenomena with some differences and analogies:

- The so-called “compassionate use” of drugs: the expression indicates non-validated treatments for personal and single use. Compassionate care is not an alternative to the consolidate paths of pharmacological trial approved in the scientific community, but rather an exception, for particular situations.
- Off-label treatment: it refers to the use of treatments in a way that differs from those authorized, with a scientific basis of efficacy and tolerability. It does not oppose traditional standards of experimentation and use of drugs, but allows, exceptionally, under medical control, the use of treatments not yet validated by healthcare regulatory authorities in cases where patients have a serious pathology without validate therapies or with validated therapies that are not effective.
- The “expanded access” to treatments: it permits patients to have access to investigational drugs and vaccines in situations where no other effective treatment is available and in conditions of emergency, for individual and social health.

These three phenomena are all related to particular situations, and this shows the difference with translational medicine, which ordinary aims to blur the boundaries between “benchside and bedside”, in order to validate therapies in a faster and safe way.

### **2.3 Informed consent in clinical/translational research: EU hard law regulations**

In the European legal framework, there is no specific regulation on translational research, but there are EU regulations on the categories to which translational research applies and which can be referred to analogically. Clinical Trials Regulation (No. 536/2014), even there is no explicit mention of translational research, implicitly promotes translational research, aiming to simplify, accelerate and harmonise the procedures of clinical trials in the European Union.

1. Low interventional clinical trial.

The Regulation streamlines the rules for clinical trials across Europe, also introducing simplified rules for so-called 'low-intervention clinical trial', providing for authorized medicines or use off-label in the presence of published scientific evidence on efficacy and safety. The starting point of European regulatory measures remains that all clinical studies on human beings must be conducted in a way that assures their protection. The quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure and the intervention poses only very limited the additional risk to the subject compared to normal clinical practice. The Regulation adds this new category of clinical trial to accelerate process for clinical trials in line with idea to promote translational research.

## 2. Clinical studies as interventional studies, and informed consent.

The Regulation establishes that 'clinical study' means any investigation in relation to humans intended to discover the clinical, pharmacological or other pharmacodynamic effects of a medicinal product; or to identify any adverse reactions; or to study the absorption, distribution, metabolism and excretion. Its aim must be ascertaining the safety and efficacy of those medicinal products (see article 2). The Clinical Trial Regulation also explains that a 'clinical trial' is a clinical study where there is an assignment of the subject to a therapeutic strategy is decided in advance and does not fall within normal clinical practice of a Member State (see article 2). The Member States must take the measures necessary to ensure a proper procedure for commencement of a clinical trial and to ensure protection to participants involved in a clinical trial. The Regulation introduced different risk categories for clinical trials.

Clinical trials are interventional studies. In interventional studies, participants are assigned to receive one or more interventions so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. For this type of clinical trials, the Clinical Trial Regulation provide for an informed, expressed, written consent. The informed consent process for clinical trials requires communication of study risks and benefits by the consent administrator so that potential research participants can decide whether or not to participate.

The assessment of the risks and benefits comprehension is a critical component of regulatory requirements for clinical trials conduct.

## 3. Non interventional studies and informed consent

Non-interventional trial means a study "other than a clinical trial" (see article 2). The Clinical Trials Regulation (see article 1) does not apply to non-interventional studies, where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The reason for excluding non-interventional trials from the scope of the European Regulation is that these trials are typically of a lower risk than interventional clinical trials.

Nevertheless, the information collected in clinical practice can become new scientific hypothesis in laboratory. In this sense, it includes the concept of translational research as a practice of transferring scientific knowledge from clinical practice to laboratory. Whereas in phase 1-4 clinical trials the efficacy of an investigational product is explored in a patient population which has been selected according to inclusion and exclusion criteria, in non-interventional trials patients are treated under real life conditions to investigate the effectiveness of a drug.

#### 4. Data base, pharmacovigilance and publication of results.

In the context of a clinical trial, the European Medicines Agency established by Regulation (EC) No 726/2004 (amended by EU Regulation No. 1394/2007) sets up an electronic database for the reporting of suspected unexpected serious adverse reactions by the sponsor. This database is a module of the database referred to in Article 24 of Regulation (EC) No 726/2004 (the 'Eudravigilance database'). Eudra marks the final step of a process through which summary clinical trial results will be made publicly available through the EU Clinical Trials Register. The investigator must report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial.

Regulatory profiles relevant to the results of the clinical trial is very important, because the failure to publish the results of the research would violate the contract with the patient established with the informed consent. Furthermore, the European citizens' health must be promoted by health services based on the results of clinical research.

#### 2.3.1 Participants' recruitment and eligibility criteria

In every clinical research, it is necessary to define exactly which patients are eligible. The main objective is to ensure that patients in the trial can be (in case of non direct benefit) a representative sample of some future category of patients to which research results can be applied.

Eligibility or inclusion criteria are the characteristic required for participation in a clinical trial (for example, age or sex). Exclusion criteria are the characteristics that mean that subject should not participate in a particular clinical trial. Depending on the type of trial and its phase, the research team will offer participating only to certain patients and will not enrol others.

##### 1. Design of the study and protocol

Previously the Clinical Trials Directive (No. 2001/20/EC) and then the Clinical Trial Regulation (No. 536/2014) explain that the objective, methodology, statistical considerations and organization of a trial must be described in a protocol. More specifically, the Directive 2005/28/EC, which lays down provisions to be applied to investigational medicinal products for human use, affirms that the protocol must provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy (see

article 4). The data relating to the clinical trial must be clearly expressed to ensure transparency of the study.

The Clinical Trials Regulation (No. 536/2014) specifies that details of each clinical trial must be contained in the protocol. Annex I specifies that the protocol must describe the objective, methodology, purpose and organisation of the clinical trial and it must include details of clinical trial. In particular, in the protocol must be indicated: a description of the subjects participating in the clinical trial (including subjects with specific needs, for example, age, gender, participation of healthy volunteers, subjects with rare and ultra rare diseases); a description of the subject inclusion and exclusion criteria; a justification for the gender and age allocation of subjects (also if a specific gender or age group is excluded from or underrepresented).

The general principle is that a clinical trial may be conducted only where the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences.

## 2. Specific gender provisions

The Clinical Trials Regulation (No. 536/2014) provides for specific provisions for pregnant or breastfeeding women participating in clinical trials, in particular when the clinical trial does not have the potential to produce results of direct benefit to her (or to her embryo, foetus or child).

More specifically, a clinical trial on the pregnant or breastfeeding woman may be conducted only if it poses a minimal risk and burden to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child (see article 33). Clinical trial on these vulnerable women can be conducted also if it does not have the potential to produce results of direct benefit to her or to her embryo, foetus or child after birth.

## 3. Minors and informed consent

With regards to minors, the Regulation specifies that clinical trial may be conducted if there are scientific grounds for expecting that participation in the clinical trial will produce a direct benefit for the minor concerned outweighing the risks and burdens; or some benefit for the population represented (indirect benefit) by the minor and a minimal risk to the minor involved.

Clinical research in minors is now extended from direct benefit for the individual to benefit for the group of patients. Parents have an important role. They have to be fully involved in the informed consent process and to feel that they are sufficiently informed.

The Regulation (EU) No. 536/2014 sets out general rules on clinical trials, but without specifying the clinical trials on vaccinations.

### 2.3.2 Obtaining informed consent

Informed consent is the process that applies to each communication to participants, from the recruitment to the conclusion of the study. It contains an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and it describes the obligation of the investigator to inform the subject about benefits and risks of the study. The informed consent can be seen as a contract at the base of relationship between investigator and patient.

- Sponsor authorization request. The Clinical Trials Regulation (No. 536/2014) specifies that before commencing any clinical trial, the sponsor must be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial. The sponsor must not start a clinical trial until the Ethics Committee has issued a favourable opinion.
- Role of the ethical committee. The responsibility of the ethics committee is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection. The ethics committee expresses an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent. All clinical trials must always be preceded by adequate pharmacological and toxicological tests.
- Phases of trial. Preclinical research is not done with people, but it involves laboratory studies (in vitro) and tests on animals. This step of the study includes an investigation of the possible toxic and/or teratogenic effects. Functions of the physiological systems are investigated, and the investigator must provide a general pharmacological characterization of the drug, with particular reference to adverse reactions (Pharmacodynamics).

After preclinical studies that provide evidence of safety, the substance is at first tested in trials involving healthy human volunteers. Since 1940s, the scientific community has drawn up a distinction in phases of clinical research, which is accepted by European laws.

### 2.3.3 Informed consent in phases I to III

Depending on the phase and the object of the clinical trials, the level of risk and its communication change. Informed consent must be obtained before procedures and treatments are performed.

#### 1. Informed consent in phase I.

The patients involved in Phase I have significant possibilities to experiment serious side effects. They must be adequately informed before they consent to participate. The duty of investigators to inform in this stage is very strict. Phase I studies assess the safety and tolerance of a drug. This initial phase of testing includes a small number of healthy volunteers (20 to 100). The study is designed to determine the effects of the drug on humans including how it is absorbed by the subject. In this step side effects are analysed.

The process of patient recruitment and informed consent is governed by laws to ensure the rights, safety, and well-being of participants. Previously the Directive 2001/20/EC and then the Regulation (EC) No. 536/2014 establish that it is necessary to make provision for the



monitoring of adverse reactions occurring during the clinical trials using Community surveillance procedures in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk.

Legal requirements are honesty regarding the nature of participation in clinical research and honesty regarding the level of the risk. Science and experimentation must demonstrate formal, ethical and methodological correctness. Patients involved in the clinical trial must represent the future category of subjects to whom the drug can be administered, but women and children are usually excluded from this phase of experimentation.

The Regulation (EU) No 536/2014 on clinical trials of medicinal products for human use introduced requirements for taking account of gender in trials, but the procedure is to involve only men in the first phase of clinical trials, with particular attention to life expectancy, performance status and organ function.

Concerning the inclusion criteria to participate in a clinical trial, the European Parliament, with the resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096(INI)), calls on the Member States, when applying Regulation (EU) No 536/2014, to use a methodological approach for clinical trials. This approach would guarantee an adequate representation of men and women.

## 2. Informed consent in phase II.

Phase II is need to confirm drug has therapeutic effect, to determine optimal dose, to determine correct frequency dosing. This second phase involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded": neither the patients nor the researchers know who has received the experimental drug.

## 3. Informed consent in Phase III

Phase III compares the effects of a new treatment with standard treatment, finding out efficacy of the drug and effects or risks and safety in the long term. It is required a large number of volunteers/ patients (several hundred or thousand) to provide significant clinical and statistical power. Concerning phase II and phase III of clinic trials, gender and age-related aspects are not addressed and there are no specific legal provisions about obtaining informed consent in these steps.

### 2.3.4 Phase IV: informed consent and pharmacovigilance

From Clinical Trials Regulation's perspective, non-interventional studies investigate various aspects of drug use including efficacy and safety under real life conditions. Phase IV of clinical trials studies the drug after it has received a Product Licence – drug marketed. Pharmacovigilance is the field of public health research that studies the effects of medicinal

products in large populations. The specific objective of this stage is to evaluate drug's long-term effectiveness and impact on a patient's quality of life. In this sense, pharmacovigilance is non-interventional research. The informed consent is also necessary for non-interventional studies. The content of informed consent in phase IV of clinical trials is different compared to that of earlier phases, but participant's participation remains informed and voluntary.

The European legal framework of pharmacovigilance for medicines for human use marketed within the EU is provided for in Regulation (EU) No. 726/2004, as amended by Regulation (EU) No. 1235/2010, and in the Directive 2001/83/EC, as amended by Directive 2001/84/EC. Title IV of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use contains the provisions applied for the authorisation for the manufacture of medicinal products as part of the requirements needed for the application for a marketing authorisation. The marketing authorization rules guarantee the quality assessment. The competent authority of the Member State issues manufacturing authorization. Pharmacovigilance is also governed by Commission Implementing Regulation (EU) No. 520/2012.

This body of legislation aims to strengthen public health through improved prevention, detection and assessment of adverse reactions. New legislation for pharmacovigilance is supported by a new guidance on good pharmacovigilance practices (GVP), a new set of guidelines for the conduct of pharmacovigilance in the EU. The pharmacovigilance legal requirements and GVP apply to all medicinal products authorised in the EU, whether centrally or nationally authorised. While risk proportionality underpins the new legislation, the requirements are generally the same for different types of product.

Pharmacovigilance is an essential part of pharmaceutical product development and commercialization. All safety aspects must be monitored properly through a systematic approach. Benefit and risk must be continually assessed as more is learned about the product through its use.

- Informed consent, in phase IV, essentially comprises a data privacy clause, there are no additional diagnostic tests or invasive procedures. The patients should report adverse drug reactions directly to the national competent authorities. The Regulation No. 726/2004 affirms that patients should be encouraged to communicate any adverse reaction to health-care professionals. The Regulation establishes that each Member State must ensure that all suspected serious adverse reactions occurring to a medicinal product are recorded and reported promptly to the Agency and the marketing authorisation holder (article 25). The Agency then forward the information to the national pharmacovigilance systems set up in accordance with Article 102 of Directive 2001/83/EC.
- The Regulation (EC) No 726/2004 introduced a number of further criteria in regard to patient information, such as: the requirement to publish a public assessment report, including a user-friendly summary of product characteristics; the basis for access to information on pharmacovigilance and clinical trials; the creation of a database on medicinal products accessible to the general public.
- If the medicinal product is already authorized in other countries, information must be given in respect of adverse drug reactions of the medicinal product concerned.

- In the case of vaccines already authorized in other countries, information on the monitoring of vaccinated subjects to evaluate the prevalence of the disease in question as compared to non-vaccinated subjects must be submitted, if available.
- These legal requirements established by the aforementioned European laws apply for clinical trials in general and they are not specific for translational research or for vaccines.

### 2.3.5. Multicultural and gender issues with regard to informed consent in translational/clinical research

Comprehension and communication are key aspects of the informed consent process. An informed choice concerning research participation depends upon a clear understanding of the potential risks and harms associated with the study.

In the European legal framework there are no specific legal provisions on informed consent in translational/clinical research with particular regard to multicultural and gender issues, as patterns which influence understanding process. However, regulatory measures that govern the obtaining of informed consent for research are focused on ensuring that research is conducted in an ethical manner and in respect for individual preferences and dignity. Laws specify that the informed consent process must be communicated in a meaningful manner to individuals, especially to vulnerable people.

In particular, the Regulation (EU) No. 536/14 affirms that the information given to the subject for the purposes of obtaining his or her informed consent must be "comprehensive, concise, clear, relevant, and understandable to a layperson". The Regulation stresses the importance of the communication and understanding process in clinical trial, but it seems to underestimate the different processes of communication and information for women rather than men.

At the level of the EU, the Lisbon Treaty, which was adopted in December 2007 and entered into force on 1 December 2009, has reiterated that respect for human rights is one of the values on which the EU is founded. The competence of the EU in the field of public health is primarily a national matter, in line with the principle of territoriality. Article 168 of the Consolidated Treaty, which is concerned with public health, encourages EU member states to establish guidelines, share best practices, and establish systems for monitoring and evaluation. The Treaty also gives legally binding force to the Charter of Fundamental Rights of the European Union. The Charter sets out the right of everyone to access preventive health care and to benefit from medical treatment.

Many factors can interact in the communication process and influence the right to access health care, for example ethnic, cultural, social, religious patterns. Understanding process can be also influenced by elements, such as health literacy, or sociocultural background of subjects involved in clinical research. The European objective is to urge member States to improve the communication process in the health field.

## 2.4 National regulations on translational research

### AUSTRIA

#### Soft law

There are no specific guidelines or recommendations dealing explicitly with translational research. However, some documents implicitly refer to it, offering an ethical framework and indications, also related to informed consent.

Austrian Bioethics Commission, Opinion on *Research on persons without the capacity to consent—with special consideration of the concept of risk* (2013)

The document highlights some important points related to translational research and informed consent:

1. the importance of medical research that has led to a significant increase in diagnostic and therapeutic possibilities for the treatment of diseases. Even if not explicitly mentioned in the document, it is possible to assert that translational research is of paramount importance to achieve breakthrough therapeutic results (from bench to bedside).
2. the relevance of the clinical research on humans and the necessity of autonomy and self-determination of the patients involved in trials as a central element in the ethical assessment of clinical research projects
3. the involvement in research of particularly vulnerable subjects, such as minors, who due to their legal status, and until they reach cognitive faculty and capacity of judgment, are unable to give consent to treatment or research procedures. The Commission underlines how this may become problematic, since research is oriented towards the future and therefore contains a certain level of uncertainty. For instance, in many research tasks, when comparing different treatment options, researchers start from an hypothesis, which means they must be uncertain whether the new treatment method under evaluation is better than other ones already validated (equipoise). The goal of research is to gain scientific certainty with regard to efficacy, tolerability and safety of treatment methods, thus providing proven therapies to future patients afflicted with the same disease.
4. Research of novel treatment methods merely builds on a scientific hypothesis, which after a certain phase of research also needs to be tested on human patients. In addition, the collection of body fluids and tissues which does not harm the physical integrity of the individual patient may also be necessary for gaining knowledge and developing new therapies, posing ethical issues of privacy and confidentiality. Hence, “the unpredictable

outcome of research is in contrast to the generally acknowledged protection criteria". This is an implicit reference to translational research.

The document distinguishes the *curative treatment*, *curative attempt* and *scientific research project*:

"In *curative treatment*, focus is on the individual's wellbeing. The purpose of treatment is to improve the individual's health condition based on the established methods of treatment.

The *curative attempt* has a similar purpose, but here the treatment is based on methods not yet standardised. It is applied when established standardised methods have shown to be ineffective and there are no established standards for the new methods. However, the sole purpose of treatment is to improve the individual patient's health condition.

Medical-therapeutic interventions in the framework of *scientific research projects* serve for the systematic review of hypotheses, such as the comparison of two principally effective substances, in order to be able to exactly determine which of the two is superior or inferior to the other one. One purpose is to provide treatment for a certain condition (potential direct benefit for the patient), the other is to obtain a general finding for medical research and subsequently for society or certain groups of persons (potential indirect benefit)."

Despite not being explicitly mentioned in this document, these distinctions can help us understand how translational research becomes a "two-way road" (from bench to the bedside and back), creating blurred boundaries between steps (pertaining to clinical research and medical practice).

5. Here the informed consent process has a pivotal role in ensuring effective benefit-risk communication between researchers/physicians and patients, in order to avoid therapeutic misconception with respect to an overestimation of envisaged benefits deriving from undergoing such interventions.

In the context of a curative treatment, the potential direct benefit of a medical intervention is prerequisite to the justification of any medical intervention. This principle can also apply to curative attempts, which are performed when all conventional medical therapies have failed. Curative attempts are thus also applicable to groups of subjects unable to give consent, as long as the intervention has the sole intention to improve the individual's health, because it can be assumed that it would be the presumed will of the person concerned. In scientific research, a potential direct benefit also plays a key role in the ethical evaluation of the trial.

Then, there are cases of "group benefit research", where the expected benefit is not directly related to the person concerned, but to the group of persons to which the individual belongs. It may only relate to persons afflicted with the same disease or disorder, but it may also include all persons in the same age category. According to the Austrian Bioethics Commission, "from an ethical perspective, the principle of group benefit shall justify medical research on

persons without capacity to consent also in cases where no direct benefit is to be expected. This is of particular importance in research projects on infants, which are regarded as urgently needed, and which would otherwise not be possible. The broader concept of social value assumes importance to identify whether a certain research project can be regarded as valuable to specific groups of people or society on the whole”.

6. However, there is general agreement that in situations with no direct benefit, the assessment and consideration of risk is of special importance. “All forms of research which are not directly beneficial to the person concerned are usually only permissible if they bear no risk or only minimal risk. For this reason, it is essential to search for objective criteria, which facilitate a safe and uniform risk assessment”. Nevertheless, balancing research interests and protection of persons involved in research studies raises a particular ethical challenge, especially when enrolling particularly vulnerable human participants, who require special protection by society.

But these precautions, which are necessary in many respects, also significantly limit the range of research options for the benefit of the groups of persons concerned and consequently deprive them of their adequate share in medical progress.

6. The role of ethics committees. The Commission recommends that “relevant criteria with regard to research projects with no or minimal risk and no or minimal burden should apply to all groups of persons, including those who are able to give consent. In any case, researchers shall demonstrate and the competent research ethics committee, in its usual review, shall evaluate whether or not a research project fulfils the aforementioned criteria (no/ minimal risk and minimal burden)”, in order to provide guarantees of high-quality medical research, which is crucial for the development of new and better therapies.

It also suggests to generally provide a clear definition of interventions with no or minimal risk and those with no or minimal burden and devises a list of “no risk—no burden” interventions (i.e. epidemiological studies, follow-up evaluation of data available from in-patient stays without further intervention, compilation of patient history data, compilation of parameters for the assessment of quality of life (i.e. pain assessment, dietary assessment etc.), non-invasive collection of other material to be examined (saliva, hair), use of surplus examination materials gathered during a diagnostic/therapeutic routine check-up, ultrasound examinations etc.); as well as a selection of minimal risk-minimal burden interventions (i.e. hearing and eye tests, venous or capillary blood sampling by finger or heel prick, lung function tests, digital non-invasive imaging techniques (e.g. chest X-ray), etc).

There is no reference to multicultural issues in translational research.

Ethics Commission of the Medical University of Vienna

As for informed consent in clinical trials, the published on its official website a standard version of informed consent in clinical studies and the necessary content to be included in the patient information, encompassing the following requirements:

- Accurate description of the goal of the clinical trial
- Illustration of alternative treatments
- Structure of the clinical trial
- Type of drug/medical device to be tested
- Indication of possible benefits deriving from participation in the clinical trial
- Description of any risks, burdens or expected side effects
- Clarifying whether concomitant medication would be necessary
- Indication of any changes in daily life needed due to participation
- Providing clear information about what to do, if symptoms, side effects or complications occur
- Explaining whether women of childbearing potential can be enrolled in the clinical trials and if a pregnancy test is required
- Description of existing conditions under which the clinical trial will be ended prematurely
- Indication of any costs or reimbursement for participation
- Mentioning the possibility for further questions to arise specifically linked to the clinical trial
- Indication of other sources of information concerning clinical trial enrolments
- Specifying whether other physicians should be informed of the participation
- Inclusion of abstract of the information sheet

#### Hard law

1. Legal framework. In Austria no single legislation covers all biomedical research. Several different acts regulate different aspects, although some of them are not covered by special regulation and generally accepted legal principles apply. The main acts concerning biomedical research are the *Drug Act* (Arzneimittelgesetz) 1983, which has been amended on several occasions (for clinical trials with a drug - AMG §42 applies) and the *Medical Devices Act* (Medizinproduktegesetz) 1996. General legal principles regarding informed consent to research on human beings require that involved subjects be informed about purposes, alternatives, nature, risks, burdens and benefits of the procedure; subjects must be provided with information about insurance and reimbursement policies.

2. Translational research. There are no specific regulations regarding translational clinical research, as it is under the regulation of drug trials. Nevertheless, non-interventional studies can be carried out if restricted to the framework of routine medical practice, thus linking clinical research and clinical practice. This means that the medicinal product must be prescribed in the usual manner in accordance with the terms of the marketing authorisation, no additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data. According to § 2 of the National Regulation on the Reporting Obligations for Non-interventional Studies, BGBl. II Nr. 180/2010, amended by BGBl. II Nr. 484/2012, a patient participating in a non-interventional study must be informed about his/her participation by the treating physician.

However, a patient information document and written informed consent is currently not required by law in this case.

3. Compassionate use. The so-called “compassionate use” (that is exceptional early access to not already validated treatments in a single patient or limited group of patients) is permitted by AMG 8a in case of unauthorized medicinal products for human use, indicated for acquired immune deficiency syndrome, viral diseases, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions. Informed consent is required and patients must be informed about the contrast and the blurred distinction between the therapeutic purpose and the goal of obtaining new knowledge through the treatment. The Authority involved is Austrian Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen, BASG).

4. Gender and multiculturalism. Clinical trials of drugs on fertile women may only be conducted or continued if pregnancy is ruled out by a negative pregnancy test carried out before and at regular intervals during the clinical trial. In the interests of protecting women and the foetus, a clinical trial of a medicinal product may only be carried out on a pregnant woman if the aim is to achieve a direct benefit for the pregnant woman or the unborn child (AMG Section 44). Concerning the valid informed consent process, gender and cultural differences are not explicitly taken into account in the definition of legal requirements about information provided and consent recording. Nevertheless, adequate and clear information must be given to the subjects involved, assessing that it has been understood. Thus, translation and cultural mediation may be used as means to fulfil those legal requirements.

## FRANCE

### Soft law

#### French National Institute of Health and Medical Research

Even if guidelines are missing on the subject of translational research, the French National Institute of Health and Medical Research (INSERM) devotes consideration to the clinical evaluation of the safety and efficacy of a new medicinal product, recalling the different and successive phases through which it is carried out (each gives rise to a different trial):

- Phase I is conducted on a small group of healthy volunteers or patient volunteers, depending on the agent evaluated. This involves testing it in humans for the first time, in order to study its fate in the body over time (kinetics) and to assess its toxicity.
- Phase II is carried out in patient volunteers. The goal is to determine the safety and efficacy of the agent. An initial step verifies the minimum effective dose, for which minor or no adverse reactions are observed. This dose will subsequently be administered to 100 to 300 patients (insofar as possible,



according to the frequency for the target disease), with the purpose of investigating any therapeutic benefit.

- Phase III evaluates the therapeutic benefit of the medicinal product on a much larger number of patients: from a few hundred to several thousand, for very common disorders, such as hypertension. The volunteers are usually split into two groups to compare the efficacy of the candidate medicinal product with a reference treatment (if one exists) or placebo (a neutral substance). At the end of these trials, and based on their results, the health authorities decide whether or not to grant marketing authorization (MA) for the investigational medicinal product.
- Phase IV: it is meant to monitor the long-term use of the medicinal product, under actual conditions of use, so as to detect any rare adverse reactions, delayed complications or even prescription bias or improper use.
- INSERM recalls that human research must meet numerous organizational and ethical criteria, controlled by law, to guarantee the safety of participants. This system is based on extensive thinking, aiming to protect persons taking part in research, whoever they may be (minors, protected adults, adults, patients or vulnerable persons, healthy volunteers), together with their data and biological specimens (blood, tissue, organs). The interests of these individuals must always prevail over scientific and social interests.
- In order for a clinical trial to start in France, the investigator must:
- receive a favourable opinion from an ethical research committees and an authorization from the French National Agency for Medicines and Health Products Safety
- inform the individuals invited to participate in the research on the study objectives, its methodology, the expected benefits, obligations and foreseeable risks, their right to refuse to take part in the study and to withdraw their consent at any time, therefore having the opportunity to end their participation in the study without any ensuing impact on their future care
- obtain written informed consent from persons agreeing to take part in the study, and ensure that they fully understand the information provided.

Moreover, INSERM works closely with patient associations to include them in the expert appraisal process for clinical research projects on human subjects. The Institute asks them to review the information leaflets and consent forms intended for volunteers invited to take part in these trials. Since 2007, the INSERM College of Reviewers association, consisting of 70 patient representatives, has primarily aimed to ensure that the information leaflet and consent form are clear, accessible and comprehensive.

As a sponsor, INSERM has recently committed, by signing a policy promoted by the World Health Organization, to disclose the results - whatever their nature - of trials on medicinal products for which it acts as sponsor. The Institute offers guidance to scientists in this process, so as to promote scientific knowledge sharing to make progress in public health and contribute to greater transparency in medical research.

The French National Consultative Ethics Committee for Health and Life Sciences (CCNE) *Opinion N° 73 on Phase I Studies in Cancerology* (2001)

The French Committee defines Phase I studies as “the first trials involving human subjects following experimentation with animals; they are an essential step before any new molecule is put to use. Their main purpose is not to seek a therapeutic effect, but to assess toxicity by determining a maximum tolerated dose. They also research possible adverse effects in both

qualitative and quantitative terms, their duration, their potential reversibility, and their possible connection to pharmacokinetic data. This data is required before proceeding to the first studies of the drug for efficacy (phase 2 trials). Phase I trials are organised according to very strict scientific protocols (recognised competence of personnel, approved premises). They entail a process of dose escalation administered to small separate groups. Subjects are generally healthy volunteers”.

However, since anti-cancer drugs used in cancerology are usually very cytotoxic, they cannot be used on healthy volunteers in phase I trials. They are administered to cancer patients for whom therapy is no longer an option, who are sometimes in fact terminally ill. Although the aim of phase 1 studies is not to pursue therapeutic effects, a study of the literature does show that therapeutic benefit may come about.

The French Committee emphasises that the key requirements of paediatric oncology research are such that phase I trials need to be performed on children suffering from specific cancers, or else to adapt the adult maximum tolerated dose, which had already been determined.

The document develops an ethical reflection on first-in-human clinical studies.

1. Physicians’ duties. The document stresses the fact that physicians have a duty to alleviate their patients’ pain and suffering, respect their dignity, and give due consideration to their best interests, but must also further therapeutic progress, and these two imperatives do not necessarily coincide. The goal envisaged for these preliminary but necessary trials, is “to evaluate tolerance and toxicity of new drugs, without seeking directly any therapeutic benefit for the participating patient”.

2. Informed consent. Information given to patients regarding the uncertainty of any benefit, the possibility of adverse effects, and ensuing risks, often leads to some confusion. More or less consciously, there is a tendency to minimise problems, in this way no truly informed consent is achieved.

It also points out that “the quality and veracity of information provided to the patient vary considerably, which may have an effect on the crucial loyalty of the doctor-patient relationship. Neither in France, nor in most other European countries, is there a standard form for the written notice of information for this type of trial”.

3. Among the main recommendations, it is noteworthy mentioning the following, with specific mention to informed consent:

- In the scientific field, the authorities should encourage and view as a priority the development of research seeking to modify the methodology of phase 1 cancerology trials, despite difficulties emphasised above, so that the risk of toxicity can be reduced, and both toxicity and efficacy can be researched jointly.
- A national model, or even a European one, for notices of information and consent forms, containing all the mandatory items, should be drafted and given to investigators to help them promote good practices. In the written material and during discussion with the patient, the doctor should provide

information on the kind of toxic event sought after; mention of modest hopes of benefit must not conceal uncertainties, nor the fact that the trial's major objective is to investigate tolerance of a new substance. The word 'treatment' should be avoided. Signing the consent form should take place several days after handing over the notice of information, and after the investigator has replied to any new or reiterated queries.

- Whenever dealing with minors, methods for offering options and obtaining consent raise particularly crucial issues, and all efforts must be made to ensure that parents do not regret any decision they may have taken.
- Improving the process of conveying information should not be limited to documents mentioned and patients concerned by these trials. CCNE recognises the essential role of intermediary played by support groups who could be urged to take more interest in this difficult problem.
- Society as a whole should be made aware of the reality and necessity of drug trials generally, and more particularly of those evaluating tolerance to a new molecule.
- Selection of patients for enrolment is an ethical issue of the utmost importance. Preference should be given to patients who have arrived at the end of their therapeutic options, but not actually at the end of their lives, so as to bypass for this type of study these particularly vulnerable people who are often willing to submit to phase 1 trials without any clear understanding of their object and scope. Choosing patients whose tumour would seem to have, according to experimental data, some chance of being affected by the new molecule, would be desirable for that to happen, phase 1 trials would need to be carried out with the greatest possible rapidity, so that a phase 2 trial on efficacy could be offered very soon thereafter.
- Enrolment in a trial confers special responsibility on not just the physician, but also on the entire health care team, who must be fully committed to the trial and ready to ensure that the patient has understood the importance of what is at stake.
- The patient's quality of life should never be jeopardized by depriving him of any palliative care he is entitled to receive. It is a fact that the rationale of such trials entails a risk that quality of life can be undermined by a series of side effects to which remedy must be provided with attentive efficacy.

There is no reference to gender or multicultural issues in translational research (for a discussion of these aspects in clinical research, see D1.3 and especially: Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé 1993, *Cooperation in the field of biomedical research between French teams and teams from economically developing countries. Report*; Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé 2003, *Disparity in access to health care and participation in research on a global level: ethical issues. Opinion n°78*).

## Hard law

1. Legal framework. In the French legal system, *Loi n°2012-300 du 5 mars 2012*, commonly called *Loi Jardé*, regulates research on human beings. Adopted by the French Parliament in January 2009 and promulgated in March 2012, then adapted with other regulations especially in 2016-2017, after the death of a person involved in a clinical trial concerning the molecule Bia 10-2474 in January 2016. In the same circumstance, five persons were seriously damaged during the trial.

This regulations aim at fixing a single framework for all research involving human beings, including both interventional and observational studies. The essential legal innovation is a

common regulatory framework for the conduct of all the studies organized and carried out on the human being in developing biological or medical knowledge, depending on the level of risk related to the research.

2. Translational research. Three sub-categories of clinical research are identified and this classification is important with regard to informed consent too, because risk-appropriate consent is required (art. L. 1122-1-1, *Code de la Santé Publique*):

- *Interventional research*: is an intervention on a person which is not justified by his/her usual medical care. The risk is more than minimal and the regulation asks for an informed, expressed, written consent. Clinical trials involving healthy volunteers are always considered as belonging to this category.
- *Interventional research* with minimal risk, the list of which is fixed by a Decree of 3 May 2017: are those related to the routine medical practice for which consent procedures can be more easy, nevertheless informed and expressed (not necessarily in written form) consent is required. The research which relates to a medicinal product for human use cannot be included in this category.
- *Non-interventional research* (observational) is defined as research in which all products are used in the usual way without additional or unusual diagnostic, treatment, or surveillance procedures. Non-interventional research also would include records research and the administration of questionnaires. All acts are carried out and all products are used without any extra or unusual diagnostic, treatment, or surveillance procedures. In this case the French law requires information and recognise a right to objection, but not an actual informed consent process, neither asks for consent in writing.

Jardé Law implementation has been developed through the Ordinance 18 November 2016 which substantially modifies the legal framework for research in France; Decree No. 2016-1537 concerning research involving the human person (supplemented by Decree No. 2017-884 of 9 May 2017 amending certain regulations concerning research involving the human person); Decree No. 2016-1538 on the Single Convention for the Implementation of Commercial Research Involving the Human Person in Health Care Facilities, Homes and Health Centers.

These provisions were supplemented by ten Decrees of 2 December 2016 regarding, in particular, the presentation of the dossier to request an opinion to the Ethics Research Committee, the content and presentation of the research protocol and the submission of the request for substantial modification. Furthermore, the above mentioned Decree of 3 May 2017 fixes the list of research involving only minimal risks and constraints.

While requirements concerning consent differ according to the nature and level of risk, which is related to the research, the content of the information due to the subject is the same. This is one of the major innovations resulting from the Ordinance of June 16, 2016, which includes interventional and non-interventional research. Researchers must inform subjects about the finality, methodology and duration of the research; expected benefits, constraints and foreseeable risks, also in case of withdrawal; possible medical alternatives; healthcare provided at the end of the study.

According to that, translational clinical research is not mentioned in French Law, but legal issues related to informed consent can be addressed also with regard to this topic. Even if

there are not relevant differences on information to provide to the subject, which is the same for each kind of clinical research, we can affirm that moving “from bench to bedside and back” (according to the definition of translational research) requires to take into account the category of research concerned: according to French law, if translational research is interventional (from bench to bedside) consent must be expressed and written; if translational research is observational, is sufficient to inform the subject and not to receive an objection; if does not involve human beings, there is no legal problem about informed consent.

3. Compassionate use. The so-called “compassionate use” (that is exceptional early access to not already validated treatments in a single patient or limited group of patients) is permitted in case of treatment or prevention for serious or rare diseases, no proper treatment is available, efficiency and security are presumed according to the scientific knowledge (art. L5121-12, Code de la Santé Publique). Informed consent is required and patients must be informed about the contrast and the blurred distinction between the therapeutic purpose and the goal of obtaining new knowledge through the treatment. The Authority involved is Agence nationale de sécurité du médicament et des produits de santé (ANSM).

4. Gender and multiculturalism. Special protection is in force for vulnerable subjects, such as pregnant or parturient women and nursing mothers. Interventional research on these subjects, even though with only minimal risks and constraints, can only be authorized if research of comparable effectiveness can not be carried out on another category of population and important benefit (direct or indirect) is expected (art. L. 1121-5 to L. 1121-8, *Code de la Santé Publique*). Multicultural issues are not explicitly taken into account, but adequate and clear information must be given to the subjects involved, assessing that it has been understood. Thus, translation and cultural mediation can be used as means to fulfill those legal requirements.

## GERMANY

### Soft law

The Institute for Research Information and Quality Assurance (iFQ) and the Berlin Institute of Health, *In search of translational research. Report on the Development and Current Understanding of a New Terminology in Medical Research and Practice* (2015)

The document highlights that “the aim of translational research is to support an efficient translation “from bench to bedside” and “from bedside to bench”, hence from laboratory basic research into clinical therapies and vice versa”, underlining its intrinsic multidirectional nature. However, organizational processes that link researchers and clinicians seem to be

particularly controversial. Up to date, no dominant model has come to fore to tackle these problems. A clear conceptual framework is also missing. Rather, a number of approaches and concepts are currently promoted by various stakeholders that highlight different aspects of translational research. Professional and public discourse on the subject now reaches well beyond the realm of medicine.

The moral dimension of translational research focuses on the lack of implementation when translation fails to occur, resulting in a shortage of effective therapies. This, it is argued in the report, costs patients' lives since promising treatments get "buried". The relevance of this dimension has been strengthened in particular by researchers and practitioners who focus on the bedside perspective (i.e. the treatment of the individual patient). The moral argument is therefore necessary to give evidence of the importance of understanding translational research as a "multidirectional enterprise, addressing efforts to move more effectively from bedside to bench and vice versa".

No reference is made to multicultural issues in translational research.

#### Hard law

1. Legal framework. Germany is a federal State and the federal law regulates medical research in general. The regulation of medical research on human subjects is not fixed by one comprehensive act, but is set by different acts. Dealing with informed consent, the most important German act is the Arzneimittelgesetz (AMG – Act on Medicinal Products), 2005, which regulates clinical trials of medicinal products on human beings. Chapter 6, section 40 of AMG sets general conditions for clinical trials and requires legal protection for subjects involved. The patient has a right to accept or reject all treatment and freely choose from alternatively available therapies with their particular risks and benefits. In order to freely decide, patient must be given all information that is relevant to freely form his/her mind concerning a specific treatment, including risks and benefits, as well as other kinds of therapy that might come into consideration. In addition to the general requirements for informed consent to medical treatment, clinical trials require a contract on the participation; specific (statutory) safety requirements and regulations; ethical means of safeguarding patient's rights such as Ethics committees.

2. Translational research. There are no rules explicitly concerning translational research, but there is an intermediate category of intervention between clinical trials and clinical practice, defined as clinical trials on a person who is suffering from a disease which is to be treated by the investigational medicinal product. Linking clinical trials and therapeutic treatments, these interventions require, in addition to the general rules for treatment, heightened requirements of indication and clinical justification, according to the findings of medical science in order to save the person's life, to restore health and alleviate suffering. Furthermore, potential direct or indirect benefit and heightened duties to conduct treatment according to scientific standards are required. Continuous monitoring on treatment to assess if it is effective and

immediate withdrawal when goals become uncertain are mandatory. In emergencies, if consent cannot be obtained, necessary experimental treatments can be carried out immediately to save the life of the person concerned, restore his/her health or alleviate suffering. Nevertheless, informed consent must be obtained as soon as possible (AMG, Chapter 6, Section 41). Nevertheless, no specific requirements apply and no decision of ethics committee is needed. For these reasons, this kind of clinical research is highly controversial and, concerning informed consent, the duty to inform the patient is heightened to avoid therapeutic misconception, that is failing the evaluation of the distinction between clinical research and clinical treatment.

3. Compassionate use. The so-called “compassionate use” (defined as exceptional early access to not already validated treatments in a single patient or limited group of patients) is permitted for administration to patients with a seriously debilitating disease or whose disease is life-threatening, and who cannot be treated satisfactorily with an authorised medicinal product (AMG, Chapter 4, Section 21.2.6). Informed consent is required and patients must be informed about the contrast and the blurred distinction between the therapeutic purpose and the goal of obtaining new knowledge through the treatment. Authorities involved are the German Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI).

4. Gender and multiculturalism. No rule, regulation, soft law or case law incorporates any gender-related differences regarding the informed consent process, nor multicultural issues are explicitly taken into account. Nevertheless, adequate and clear information must be given to the subjects involved, assessing that it has been understood. Implicitly, law requires to consider gender or multicultural aspects in providing information about risks and benefits. Concerning clinical trials on pregnant women or nursing mothers, Medizinproduktegesetz (MPG 2002) at Section 20 requires direct benefit and minimal risks.

## ITALY

### Soft law

Ministry of Health National Programme for Health Research (PNRS 2017-2019)

There are no specific ethical guidelines or recommendations on translational research. Nevertheless, an explicit reference to translational research can be found in the Italian Ministry of Health National Programme for Health Research (PNRS 2017-2019), which promotes initiatives focusing on knowledge transfer, fostering the implementation in clinical practice of research results, obtained both from state-funded research and the international scientific community. The Italian Ministry of Health recognises the paramount importance of

actions aimed at innovating professional behaviours and the organization of services, in ways that improve quality levels of the latter, thanks to the available scientific knowledge, and emphasizes the need to build on existing best practices in translating research outcomes into clinical practice.

Moreover, the necessity to fund translational research through the National Health System is clearly stressed in the document, highlighting the fact that, at the global level, basic research develops at a significantly higher pace than clinical research. Therefore, it is clearly stated that, in order to pursue innovative clinical research, we should not follow only the traditional path (“from bench to bed”), which starting from preclinical research can then become successful in identifying new treatments, diagnostic procedures etc.; on the contrary, evidence shows that attempting to find innovative responses to unsolved clinical dilemmas is much more productive in achieving innovation. This process (“from bed to bench”) facilitates the use of innovative scientific and technological knowledge to tackle real clinical problems. The Italian Ministry of Health acknowledges the need for a collaborative and interdisciplinary approach to translational research (where professionals share different skills required in translational research, i.e. expertise related to cell biology, animal models, epidemiological, diagnostic and therapeutic studies, patient and public health management). Hence, this process requires a bi-directional system (from bench to bed and backwards).

#### Italian National Bioethics Committee (NBC)

The NBC has developed ethical reflections on informed consent in many documents; some of them contain also references that, even if not explicitly mentioning translational research, deal with specific circumstances in clinical trials.

#### *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situations, 2012*

The document addresses the ethical issues of randomised clinical trials on ill or injured patients, adults or minors, who are unable to express their timely informed consent. The Italian Committee considers specific cases where treatment usually exists, but it is not effective and unsuccessful in improving the prognosis of the patient. Therefore, depriving human subjects of the possibility to participate in clinical trials would, on one hand, take away the chance for benefiting from experimental interventions and improving their health condition, and on the other, halt the therapies available from being improved for patients in the future.

In emphasising the primary need to protect the patient’s rights, safety and wellbeing, the Committee justifies the acceptability of clinical trials in emergency situations, whenever the patient is incapable of providing his/her valid informed consent and in the absence of a legal representative, under the following conditions: the approval of a protocol – based on strong experimental evidence – by an ethics committee set up ad hoc, independent, composed of physicians and other health care professionals working in the field, legal experts, patient



rights' representatives and bioethicists; the ascertainment of any possible wish opposing the experimentation previously expressed by the patient; the request for a "deferred consent" by the patient in case he/she regains capacity or by the legal representative, should the incapacity continue; the publication of the results (specifying positive or negative findings) of the trials to avoid unnecessary duplications.

*Single patient care and non-validated treatments (the so-called "compassionate use"), 2015*

The document deals with the therapeutic treatments not yet validated by regulatory authorities, taking a further step in the analysis of the different aspects of the right to health, from freedom of care to informed consent, and the doctor-patient relationship. The document specifically focuses on the "the use of theoretically validated products, whose effectiveness and safety for a specific use has not yet been verified".

The document underlines the fact that the patient's right to treatment and therefore to the protection of health, is first and foremost, the right to receive treatment approved after rigorous experimentation according to the methodological and ethical criteria shared by the scientific community and regulated by the legal system. The general rule is that the administering of non-validated treatments should take place "only as a well-motivated and strictly monitored exception when faced with a life threatening situation or the particularly serious nature of a disease, there being no recognised effective alternative for treatment and improvement of the quality of life of the patient in order to prevent deterioration".

In this context, two situations are mentioned: The first, in which the patient might have access to a treatment path for which experimentation on humans has already begun, and for which at least phase I has been completed; The second, in which no trials on human beings have started.

1. Compassionate care. In the first case (i.e. with evidence of no harmfulness) the patient could have access to "compassionate care". It is therefore possible that in the course of a clinical trial the drug, within highly specific conditions, may be used prior to being approved as a compassionate treatment. This would be a form of early access, extended to the sick in exceptional circumstances still to be accurately established, and which should however take place in a strictly controlled manner, both by the relevant authorities through the treating physicians, and also possibly by patient associations. In this way it could give rise more easily to a virtuous circle of information regarding the entire community of patients suffering from the same disease. This early access includes established criteria: the purpose would be to speed up access for patients who do not have an alternative, when the trial has already concluded Phase I and therefore there has been recognition of drug tolerability, so as to justify continuation.

2. First in human trial. The second situation is certainly the most problematic one, which usually occurs for rare diseases, where no regular experimentation is under way or reasonably foreseeable in the near future, because it is too costly for pharmaceutical companies,

considering the small number of sufferers. The problem arises when the patient in this situation consciously requests a therapy, for which there is no evidence of the absence of harmfulness.

3. From the key ethical issues raised, the NBC puts forward the following recommendations:

- It suggests replacing the expression “compassionate care” with the alternative proposal of “non-validated treatments for personal and non-repetitive use”, in order to avoid confusing the former expression with legitimate feelings of empathy towards those who are seriously and incurably ill
- Access to non-validated treatments (namely allowing exceptionally, and on the basis of a medical prescription, to resort to methods of treatment not yet approved by the regulatory authority when the patient is diagnosed with a serious disease, for which there is no validated treatment, or when available treatments have not been effective) should be exceptional, and only in the absence of validated therapies, at the express and conscious request of the patient, in cases of extreme urgency and emergency for patients with a life threatening condition; such treatments can never be an explicit or surreptitious alternative to clinical experimentation
- The administration of these treatments must refer to specific indication and normally be based on multiple reasonable scientific evidence (i.e. data published in specialized magazines with international circulation and “peer review” evaluation which include at least robust and evident results regarding animal testing for efficacy and toxicity and possibly with Phase I results on human beings).
- This therapeutic prescription cannot only come from the treating physician but must receive the approval of the Ethics Committee in whose area of expertise the request pertains. In addition, the support of qualified specialists for the diseases for which compassionate treatment is requested is necessary preferably in the form of expressed authorization by the specific panel, designated by public health institutions called on to express an opinion in a short time. In the event that the patients concerned are minors these panels must provide for the presence of neonatologists or paediatricians with proven experience in the age group concerned.
- It is necessary to avoid both conflicts of interest for those who are prescribing or administering or authorizing the treatment, as well as elements relating to possible speculation of an economic and industrial nature.
- The composition of the products used for the treatments must not be secret, be they synthetic or biological in origin. All results both positive and negative must be made public.
- Since it is a request for non-validated treatment, it obviously cannot be binding on the physician.
- For patients who want to have access to a “compassionate” therapy there must be the guarantee of receiving complete explanations on the potential dangers of this type of treatment.
- The cost of the non-validated drugs normally must be borne by the manufacturer, while the relative monitoring must be headed by the specific facilities and public health institutions.
- Exclusively under these conditions can “compassionate” treatment be considered ethically acceptable and enshrined in the general right to health care.

#### *Opinion on Ethical issues in genome editing using CRISPR/CAS9, 2017*

This Opinion discusses the controversial ethical issues surrounding genome editing using CRISPR/CAS9 and, in this context, it debates on the complexity of providing a clear-cut distinction between basic and clinical research.

The NBC particularly recalls that “biomedical research can be subdivided into types classified with various conventional denominations. The term “basic research”, generally opposed to

"clinical research" presupposes research exclusively aimed at gaining knowledge, and can refer both to the study of gametes and embryos in the laboratory (in vitro) and to embryos in the uterus (in vivo). Several international documents also refer to a third type of research, the so-called "preclinical" research, for which it is difficult to identify a unique definition, both in terms of its purpose and object, since it may relate to the experimentation both in the laboratory and on the human body. The distinctions "in vitro" and "in vivo" sometimes correspond, respectively, to "basic research" and "clinical research", but often this is not the case, and in "clinical research" certain types of "research with biological materials of human origin" are included" (NBC 2017, 14).

No reference is made to gender and multicultural issues in translational research (for a discussion of these aspects in clinical trials, see Deliverable D1.3 and particularly: Italian National Bioethics Committee (NBC) 2008, *Opinion on Pharmacological trials on women*; Italian National Bioethics Committee (NBC) 2011, *Opinion on Pharmacological trials in developing countries*; Italian National Bioethics Committee (NBC) 2017, *Opinion on Migration and Health*).

#### Hard law

1. Legal framework. Decreto Legislativo 211/2003 and Ministerial Decree 21<sup>st</sup> of December 2007 (Ministry of Health) state detailed regulation on clinical trials. Information provided must comply with the rules fixed by the international and European legal framework, as well as by the Good Clinical Practice standards. The subject must be duly informed about the research's nature, duration, significance, implications, risks, burdens and benefits.

2. Translational research. Translational research is not mentioned in Italian hard law regulation nor specific rules are provided for low risk research. Decreto Legislativo 211/2003 does not apply to non-interventional studies, defined as those where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation, no additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data. In this specific case, even if the risk is minimal, the Italian regulation concerning informed consent is the same as for interventional studies (art. 2.3 Circolare Ministero della Salute n. 6/2002).

3. Compassionate use. The so-called "compassionate use" (that is exceptional early access to not already validated treatments in a single patient or limited group of patients) is permitted for diseases with no therapeutic choice. Three types of medications can be included: innovative drugs authorized for sale abroad, but not in Italy; unauthorized drugs which underwent clinical trials; drugs to be used for a therapeutic indication different from those authorized (off-label use). Regulations applied are Law no. 648/1996, Law no. 94/1998, Decreto legislativo 219/2006, Law 57/2013, Law 79/2014, Ministerial Decree of 16th of January 2015 (Ministry of Health) concerning "advanced therapy medicinal products prepared on a non-repetitive basis" and Ministerial Decree (Ministry of Health) of 7h September 2017

on the therapeutic use of drugs undergoing clinical trials. The Informed consent is required and patients must be informed about the contrast and the blurred distinction between the therapeutic purpose and the goal of obtaining new knowledge through the treatment. Authority involved is Agenzia Italiana del Farmaco (AIFA).

4. Gender and multiculturalism. Concerning the valid informed consent process, gender and cultural differences are not explicitly taken into account in the definition of legal requirements about information provided and consent recording. Nevertheless, adequate and clear information must be given to the subjects involved, assessing that it has been understood. Thus, translation and cultural mediation may be used as means to fulfil those legal requirements.

## SPAIN

### Soft Law

There is no explicit reference to “translational research” in Spanish law. Nevertheless, there is an extensive regulation (hard and soft law) on clinical trials with medicinal products, inasmuch as the Spanish government had already implemented the Clinical Trials Regulation 536/2014, by the Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry.

According to this regulation, the Spanish Agency of Medicines and Medical Devices (hereinafter AEMPS) and the Ethics Committees for Clinical Investigation accredited for assessment of studies with medicinal products (hereinafter CEIms) must evaluate, monitor and authorize clinical trials development in Spain.

The Spanish Agency of Medicines and Medical Devices issued a *Document of Instructions for Clinical Trials Development in Spain* (23 June 2017), and, as Annex VIII to this document, a *Guide for the correct elaboration of a model of patient information sheet and informed consent form* (PIS/ICF) was provided (18 April 2017). The Document of Instructions for Clinical Trials Development in Spain provides information about practical issues of implementation of the new legal regulation, and covers the aspects not developed by Royal Decree 1090/2015. This document is complementary to the *Memorandum* (2016) that summarizes the agreements reached between de AEMPS and CEIms in accordance with article 18 of Royal Decree 1090/2015.

The *Document of Instructions* describes the phases of clinical research, distinguishing:

- Commencement of clinical trial: the date on which it is considered that the first centre is ready to begin the recruitment.
- Inclusion of First subject: the date of the firm (in Spain) of the informed consent of the first selected subject (or his/her legal representative) to participate in the clinical trial.
- End of recruiting: the date of the end of the selection of subjects in Spain.
- End of trial: Date of the last visit of the last patient.
- Final report at REec on website of ECM

The investigator has the duty to publish these phases at the Spanish Clinical Studies Registry (hereinafter REec), with a maximum deadline of 15 calendar days after the date of commencement of a new phase.

*Special requirements on informed consent* are dealt with in the *Guide* for the correct elaboration of a model of patient information sheet and informed consent form. The Guide contents specific indications about the information to be contained both in the information sheet and in the informed consent form, and about the mistakes should not be made when elaborating both documents, including notably these aspects:

- Voluntary participation
- Purpose of the study
- Description of the study
- Activities of the study
- Risks and discomfort arising from your participation in the study
- Possible benefits
- Pregnancy warning (In case of participation of women of childbearing age or male patients with couples of childbearing age there must be a specific section on pregnancy or breastfeeding).
- Alternative Treatments
- Insurance
- Personal data protection
- Expenses and economic compensation
- Other relevant information
- Treatment after the end of the clinical trial
- Contact in case of questions
- Clinical studies on minors
- Collection and use of biological samples
- Sub studies directed towards all participants in the general study or directed towards a specific sub-population (in this case, an information document must be written to the specific patient of the sub-study, independently of the general study).
- Participant Consent Form
- Informed Consent of Participant Before Witnesses

The *Guide* also contains specifics regulations about *risk communication*, stipulating that patient information sheet “must describe the risks and discomfort of the tests which are carried out as a result of the study. Avoiding excessive technicalities and drafting in unnecessary details but make it clear if visits are lengthened by procedures derived from participation in the study such as questionnaires, kinetic samples, etc.”

There are not properly gender related aspects regarding to informed consent. The Guide sets out some recommendations about pregnancy and breastfeeding. Thus, the information sheet and the informed consent form “must include the known risks of the drug on the foetus, and if not, state that they are unknown. When necessary must mention the need to take contraceptive measures, as specified in the protocol.

## Hard Law

1. Legal framework and translational research. As has been noticed, there is no explicit reference in Spanish law to the expression “translational research”. But the concept is already implicit in the Act 14/2007, of 3 July, on biomedical research, which starts by establishing that “biomedical research and the health sciences are a key element to improve the quality and life expectancy of the citizens and to improve their well-being”.

However, this Act excludes from its scope clinical trials with medication and the implantation of organs, tissues and cells, which shall be regulated in a specific regulation. This regulation is currently, for clinical trials with medication, the *Royal Decree 1090/2015, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry*, according to which the supervision of clinical trials with medicinal products shall correspond to the AEMPS, in coordination with the Ethics Committees for Investigation accredited for assessment of studies with medicinal products.

Every clinical trial needs the positive assessment of both the Spanish Agency of Medicines and Medical Devices and the CEIm. The AEMPS integrate the assessment of one and the other into a single opinion per clinical trial, valid throughout the Spanish State (article 11 of RD 1090/2015).

A clinical trial may only be conducted when the CEIm and the Spanish Agency of Medicines and Medical Devices have considered that all of the following conditions are met:

- The clinical trial is ethically and methodologically sound and is designed to obtain reliable and robust data.
- The anticipated benefits for the subjects or public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored. However, the rights, safety, human dignity, and well being of the subjects prevail over any other interest.
- Freely given informed consent is obtained and documented from each trial subject before the subject is included in the trial
- The rights of the subjects as regards their physical and mental integrity, privacy and the protection of the data concerning them are safeguarded in accordance with Organic Act 15/1999, of 13 December, on Personal Data Protection, and its development regulation, as well as European regulations in force on this matter.
- The clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the trial subjects and both the level of risk and the degree of discomfort are specifically defined in the protocol and constantly monitored.

- The medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor, a qualified dental practitioner or any other healthcare professional, always in accordance with their competencies to provide this necessary care.
- The trial subject or, where the subject is not able to give informed consent, his/her legally designated representative has been provided with the contact details of an entity where further information can be received in case of need. In the case of persons with a disability, this supplemental information shall be provided according to the rules established by the design for all principle, so that it is accessible and comprehensible to them.
- No undue influence, including that of a financial nature, is exerted on trial subjects to participate in the clinical trial.
- The insurance or equivalent financial guarantee has been arranged, or the coverage specified in article 9.4 for "low-intervention clinical trials" is available.

As far as *informed consent* is concerned, the Royal Decree adopts the following definition: "A subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial" (article 2, w).

As regards to the *general requirements of informed consent*, the R.D 1090/2015 refers to the provisions of article 29 of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014, and articles 8 and 9 of Act 41/2002 of 14 November, Regulating patient autonomy and rights and obligations of information and clinical documentation (express, written consent is necessary; exceptions, limits and representation).

The new regulation pays special attention to the following issues:

- Information: All participants, but, particularly, patients with special vulnerability shall be informed of the routes of access to the normal clinical practice for their pathology (art. 4.4.).
- Revocation: the participant may revoke his/her consent at any time, without giving a reason and without it resulting in any detriment or responsibility for the person participating. (Art. 4.5)
- Biological samples: When collection of biological samples is envisaged in the clinical trial, the potential participant must be informed about the provisions with regard to the future use of the samples. (Art. 4.6).
- Clinical Trials to be conducted only in Spain: the investigator may be allowed to obtain informed consent by the simplified means set out in paragraph 2 of article 30 of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 (art. 4.7).

As far as *specials requirements of informed consent* are concerned, particular references are made to:

- Disabled persons: When the person who is to give consent is an disabled person, the information shall be provided in appropriate formats in accordance with the rules established by the design for all principle, so that it is accessible and comprehensible for them, and the pertinent support measures shall be agreed so as to facilitate their ability to provide their own consent (art. 4.2)
- Minors or incapacitated persons: Where consent has been given by their legally designated representative, when their capacity to give their consent has been attained or recovered, their consent

must be obtained to continue participating in the clinical trial (art. 4.3). Prior informed consent of the parents who hold custody or of the legal representative of the minor must be obtained, and the minor, if under 12 years of age, must be heard if the minor has sufficient judgment. The informed consent form of the parents shall be valid provided it is signed by one of them with the express or tacit consent of the other, which should be adequately documented, as stipulated in article 156 of the Civil Code. When the subject's condition allows, or in any case when the minor is twelve years of age or older, the subject must also give his/her consent to participate in the trial.

2. Gender and multiculturalism. As we have noted before, there is not regulation about gender related-aspects regarding to informed consent, but only rules concerning pregnancy and breastfeeding (art. 8).

## UNITED KINGDOM

### Soft law

#### Medical Research Council (MRC)

Efforts for strategically framing and implementing translational research funds have been particularly strong in the UK as the MRC launched its program entitled “Translational Research Strategy”. Since then translational research has evolved as an important part of MRC’s strategic program, that is, making “translational research a key part of core business, including the establishment of dedicated funding schemes to support this research” (Medical Research Council 2014). In the strategic program of the MRC, translational research is now associated with almost all stages of MRC funding. Its major goal is to “target funding towards translational projects that require an interdisciplinary approach and a critical mass of researchers to get therapies to the point of clinical testing” (Medical Research Council 2014). To achieve the goals assigned to translational research, the MRC aims at fostering partnerships between research institutions (Medical Research Council 2014), orienting researchers towards translational research (Medical Research Council 2014), and strengthening transfer activities in health research (Medical Research Council 2014).

However, there are no specific guidelines shedding light on the ethical issues stemming from translational research.

#### Nuffield Council on Bioethics

Concerning blurred boundaries between research and treatment, the Nuffield Council on Bioethics has dealt with the topic of innovative or experimental treatments, which may be provided outside the context of research, in the report of 2015 on *Children and clinical research: ethical issues*.



The Nuffield Council stresses the fact that, wherever possible, innovative therapies of any kind should undergo properly evaluated research. Nevertheless, there may be exceptional situations for which novel treatments outside the context of research is appropriate (i.e. in cases of “compassionate use”). In these specific cases, health professionals have the duty to make sure that the information about the outcome of treatment and the clinical course of the patient’s condition is collected and made publicly available (e.g. through a registry or publication).

In addition, The Nuffield Council recommends that “the Royal College of Paediatrics and Child Health takes the lead with other Royal Colleges and relevant professional bodies in exploring how best to ensure that information as to the outcomes of ‘innovative’ or ‘experimental’ treatment given to children or young people outside the context of research is properly documented and made available to others concerned” (The Nuffield Council on Bioethics, 2015).

#### Hard law

1. Legal framework. In the UK legal system there is a statutory instrument concerning clinical trials, *The Medicines for Human Use (Clinical Trials) Regulations No. 1031/2004*, amended in 2006 and 2008 by S.I. No. 1928/2006, 2984/2006 and 941/2008. Specific norms concerning informed consent to both clinical practice and clinical trials are included in the *Mental Capacity Act 2005* and common law developed by judges through decisions of courts (Chatterton v Gerson, 1981, 1 All ER 257; Montgomery v Lanarkshire Health Board, 2015, UKSC 11).

The general principle is that informed consent must be freely given and obtained from the subject before involvement in the procedure. Information must be provided about the nature, significance, risks and implications of the trial. Subsequently, any new relevant information should be communicated to the participants, if it could influence their decision to continue participation in the research. Subjects involved have the right to have an interview with a member of the investigating team to discuss and better understand all the aspects and the conditions of the trial. To provide written information is not a legal requirement in clinical trials, but is strongly recommended. However, informed consent to clinical trials must be obtained in writing and the related process must be approved in advance by an ethics committee. The subject may revoke informed consent at any time without being exposed to harm.

Great importance is given to information concerning risks, benefits and reasonable alternatives, in addition to information concerning the nature, significance and scope of the trial. This means that information and time spent during the interview should be proportionate to the risk: the more interventional is the study, the more the information should be detailed. The current UK legal framework allows a risk-related approach in obtaining informed consent to clinical trials and guidelines are based on a three-level risk

categorisation distinguishing trials with risks no higher than that of standard medical care; trials with risks somewhat higher than that of standard medical care; trials with risks markedly higher than that of standard medical care, which need to be justified with pre-clinical and clinical evidence.

2. Translational research. There is no specific regulation on translational research, but among the low-risk clinical trials there are studies linking clinical research and clinical practice, defined as “pragmatic trials”, comparing the effects of validated therapies. In that case, the amount of information provided can be reduced proportionally with reference to low risks and levels of burden. However, no pressure must be done to take decision quickly and the patient must be free to take the time needed and ask for more information, even if he is just requested to undergo a standard treatment allowing data to be used for research. The informed consent must be obtained in writing also in this case.

3. Compassionate use and innovative treatments. In 2016 the UK government passed the Access to Medical Treatments (Innovation) Act 2016 (ATMTI Act 2016). The scope of the ATMTI Act 2016 is “to promote access to innovative medical treatments (including treatments consisting in the off-label use of medicines or the use of unlicensed medicines)”, defined as “medical treatment for a condition that involves a departure from the existing range of accepted medical treatments for the condition”. The use is permitted if there is a good clinical evidence about effectiveness and safety of treatments. A public national database ensures the effective collection and dissemination of information about innovative treatments. Nevertheless, according to common law rules (see above), patients must be informed about the contrast and the blurred distinction between the therapeutic purpose and the goal of obtaining new knowledge through the treatment.

4. Gender and multiculturalism. Concerning the valid informed consent process, gender and cultural differences are not explicitly taken into account in the definition of legal requirements about information provided and consent recording. Nevertheless, as a general principle, adequate and clear information must be given to the subjects involved, assessing that it has been understood. Thus, translation and cultural mediation may be used as means to fulfil those legal requirements.

### 3. Third section – Informed consent and vaccination

#### 3.1. Experimental and validated vaccines: international recommendations and guidelines.

##### 3.1.1 Experimental vaccines

Clinical trials for experimental vaccines can be considered part of translational medicine, as an example of clinical research involving humans. There are only few guidelines for first-in-human trials with specific reference to vaccines.

WHO, *Guidelines for good clinical practices (GCP) for trials on pharmaceutical products* (1995)  
The document contains useful reference to informed consent in clinical trials:

1. Informed consent is an important part of the review of a clinical trial by the ethic committee. The ethics committee has to review in particular: the means by which trial subjects will be recruited, that the necessary or appropriate information will be given, and that consent will be obtained. WHO Guidelines reminds that this is particularly important in the case of trials involving subjects who are members of a group with a hierarchical structure or another vulnerable group.
2. Informed consent:
  - should be given in a language understandable by the subject, both in oral and written form;
  - should be appropriately recorded and documented either by the subject's dated signature or in agreement with local laws and regulations by the signature of an independent witness who records the subject's consent;
  - should be obtained with careful considerations from members of a group of hierarchical structure – such as medical, pharmacy and nursing students, hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. In such cases the willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of the hierarchy in case of refusal to participate.
  - in a non-therapeutic study, i.e. when there is no direct clinical benefit to the subject, consent must always be given by the subject and documented by his or her signature;
  - any information that becomes available during the trial which may be of relevance to the trial subjects must be made known to them by the investigator.

The protocol should state when and by whom such information will be provided, and how the provision of information should be recorded.

The investigator should also supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about contact person(s) to refer to in an emergency situation. This aspect confirm what mentioned above about the

ethical relevance of the relation among the researcher (one or more) and the subjects of the trial.

WHO, *Guidelines on clinical evaluation of vaccines: regulatory expectations* (2004)

In the document, which has been also recalled in 2005, WHO underlines that:

- care should be taken to identify the target population correctly;
- no subject may be included in a clinical trial without proper informed consent in writing. Informed consent for children should be obtained from their parent or guardian;
- specific inclusion criteria (age, geographic area, examined by the study physician and able to give their signed informed consent) and exclusion ones (if population don't meet the inclusion criteria, if a move from the area of the study is planned during the period of the follow up, social/language difficulties) must be followed in the trial;
- the approval of the appropriate independent ethics committee must be obtained *before* the start of the trial.

Gender, vulnerable groups:

1. Special attention also should be given to the ethical considerations underlying testing of vaccines in healthy infants, children, pregnant women and the elderly.
2. In the document is clarified that human challenge studies are appropriate only for selected diseases that have no serious complications or long-term sequelae and for which successful treatment is available. Such studies can provide valuable information on the pathophysiology, clinical manifestations, diagnosis, immunology, treatment response and most importantly protective efficacy of vaccines.

WHO, *Global Vaccine Action Plan* (GVAP), 2011-2020

To achieve the implementation of the Global Vaccine Action Plan (GVAP), WHO's strategic goals for vaccines for the period 2015-2030 are to promote the development of new vaccines and vaccine delivery technologies to meet public health priorities; to establish norms and standards for vaccines and delivery technologies; to ensure vaccines and delivery technologies are of assured qualities. Based on SAGE (Strategic Groups of Experts on Immunization), WHO issues global policy through vaccine position papers, published with open access in the *Weekly Epidemiological Record*.

About clinical evaluation of vaccines, the World Health Organization (WHO), through considerable international consultation, develops Recommendations and Guidelines on the production and control of vaccines and other important biologicals and these form the basis for assuring the acceptability of products globally.

For newly developed products, specific WHO or national pharmacopoeia requirements may not be available and a national regulatory authority will need to agree on specifications with the manufacturer on a case-by-case basis during the evaluation of products for clinical trials and for licensing.

WHO, *Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO*, 2014

WHO held and reported discussions regarding ethical issues in the evaluation of Ebola vaccines, regarding informed consent and whom priority recipients might be. The document stresses that “in the particular context of the current Ebola outbreak in West Africa, it is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention”. In this report for the WHO, ethical, scientific and pragmatic criteria are underlined and it is recommended transparency about all aspects of care, so that the maximum information is obtained about the effects of the interventions, fairness, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity, involvement of the community and risk–benefit assessment.

If and when unproven interventions that have not yet been evaluated for safety and efficacy in humans but have shown promising results in the laboratory and in animal models are used to treat patients, those involved have a moral obligation to collect and share all the scientifically relevant data generated, including from treatments provided for “compassionate use”.

#### Multiculturalism

The report recommends that, as consent is of paramount importance, information should be provided in easy-to-understand, culturally appropriate language. For minors, assent should be obtained whenever possible, in addition to the consent of the parents or of the guardian.

EGE, *The ethical implications of new health technologies and citizen participation*, 2015

EGE recalls the 2014 outbreak of Ebola in Africa as an example of expanded access to treatment: in response to this challenge WHO convened a consultation to consider and address the ethical implications of use of unregistered treatments. Aside from scientific criteria, certain ethical criteria must guide the use of such treatment: transparency, informed consent, freedom of choice, confidentiality, respect for individuals, preservation of dignity, fair distribution and involvement of the community. In addition, all scientifically relevant data from this intervention should be collected and shared to establish the safety and efficacy of the intervention.

CIOMS *International Ethical Guidelines for Health-Related Research Involving Humans* (2016)

The document stresses the topic of risk of harm in the context of medical research as far as vaccines are concerned:

- some risks in vaccine experimentation cannot be justified, even when the research has great social and scientific impact and even when competent adults have given their voluntary, informed consent to

participate: for example, in a study that involves deliberately infecting healthy individuals. The research must ensure that risks are reasonable;

- before undertaking research in a community without the capacity of ethical evaluation of the research by independent ethical committees, sponsor and researchers should have a plan describing of do the contribute to promote local capacity concerning ethics;
- widespread emergency use of unproven agents (for example in the case of contagious infectious diseases) must be avoided;
- without scientific validity, the research must not be conducted;
- in general, when it is not possible or feasible to obtain the informed consent of participants, research interventions or procedures that offer no potential individual benefits must pose no more than minimal risks.

## Vulnerable groups

In Guideline 18 (Women as research participants), it is underlined that much remains unknown about the safety and efficacy of most drugs, vaccines, or devices used by women in medical practice, and this lack of knowledge can be dangerous. It is intended that knowledge with a specific gender approach should be implemented.

Guideline 21 invites researchers, sponsors, relevant authorities, and research ethics committees to determine in advance of initiating a cluster randomized trial whether it is required or feasible to obtain informed consent from patients, health care workers, or community members in certain studies and to determine whether requiring informed consent and allowing refusal to consent may invalidate or compromise the research results.

## Multiculturalism

CIOMS highlights the importance of including cultural aspects in the informed consent process. In addition to content of recalled above Guideline 7 (*Community Engagement*) on cultural aspects CIOMS specifically recommends that:

- with some populations, local language may be used to facilitate the communication of information to potential participants; sponsors and researchers must use culturally appropriate ways to communicate information necessary for adherence to the requirements of the informed consent process; the project must include any resources needed to ensure that informed consent can be properly obtained in different linguistic and cultural settings (see Commentary on Guideline 9, *Individual capable of giving informed consent*);
- as far as research in disasters and disease outbreaks is concerned, communities should be actively engaged in study planning in order to ensure cultural sensitivity, while recognizing and addressing the associated practical challenges (Guideline 20, *Research in disasters and disease outbreaks*);
- Research Ethics Committee must include community members, who can represent the cultural values of the participants in the research (see Guideline 23, *Requirements for establishing Research Ethics Committees and for their review of the Protocol*).

EMA, Committee for Medicinal Products for Human Use (CHMP), *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products* (2007, first revision 2017).

Risk assessment in first-in-human trials for vaccine is specifically regulated by this document. The overall safety of vaccines is corroborated by the fact that during decades of vaccine development and application, cases of severe damage caused by the products were uncommon; in general, vaccines have an excellent safety record.

Nonetheless, the first-in-human clinical trial is a critical turning point between preclinical studies and first human exposure and subsequent larger clinical trials in hundreds or (for many vaccines) thousands of subjects. For sponsors, relevant risk assessment for first-in-human clinical studies means careful design and conduct of studies that reduce potential risk to humans. In addition, the target population for vaccine trials is healthy volunteers and this requires special carefulness concerning benefit/risk assessment.

A balanced approach for first-in-human studies of a novel vaccine candidate is crucial to ensure safety of the participants in the trial.

The calculation of a safe starting dose is a central aspect for a first-in-human trial for vaccines. Going beyond the classic approach to calculate risk for a classical medicinal product (the NOAEL approach, based on toxicity in the relevant animal model specifically on the no-observed-adverse-effect-level), the EMA Guideline in 2007 recalled an alternative approach, a calculation based on the minimal-anticipated-biological-effect level (MABEL), the dose level at which a minimal biological effect in human is expected by in vitro or in vivo data. These two principles might require very careful adaptation; the definition of a starting dose for a novel vaccine might not be straightforward and indeed “automatic” use of the MABEL approach might lead to misleading results.

Vulnerable groups:

The Guideline highlights that:

- for vaccines that target children and/or women of child-bearing potential, the influence on the reproductive system has to be explored. Here, different animal models might be defined as ‘relevant’ compared with the other nonclinical studies.
- reproductive toxicity includes male and female reproductive capacity as well as the possible influence of transferred genes on the development of the embryo/foetus during pregnancy. This might indeed be an issue, given the complex changes to the maternal organism during pregnancy, including maternal-foetal exchange (hormones, antibodies and so forth). Therefore, the possible influence on foetal development (bone structure, central nervous system, organs and so forth) has to be closely surveyed as well.
- first use in a paediatric population is a particularly critical step that needs careful consideration with respect to additional animal studies that might potentially be required (juvenile animals), further dose reduction and different dosing schemes. In addition, studies in children regardless of age are ethically difficult if no comparator yet exists and the disease to be prevented is at the same time not life threatening. Thus, justification of the trial design has to be well-supported, covering the availability of a comparator (at least established medicinal use), impact and epidemiology of the disease as well as resulting age escalation/ de-escalation planned.

### 3.1.2 Validated vaccines

WHO, *Global Vaccine Action Plan (GVAP)*, 2011-2020

In the document there are six principles that can realistically and effectively guide the full spectrum of immunization activities throughout the Decade of Vaccines (2011–2020). The principles are: country ownership (countries responsibilities for immunization), shared responsibility and partnership (responsibility for immunization is personal, of the community and governmental), equity (equitable access to immunization), integrity (strong immunization system as part of public health system), sustainability (informed decisions, implementation strategies and financial investments), innovation (improvement and innovation in research and vaccines development).

WHO, Global Advisory Committee on Vaccine Safety, *Safety of Immunization during Pregnancy. A review of the evidence*, 2014

#### Gender

In 2014, the WHO Global Advisory Committee on Vaccine Safety issued a document on *Safety of Immunization during Pregnancy*, in which it discusses key issues relating to the fact that vaccine-preventable infectious diseases are responsible for significant maternal, neonatal, and young infant morbidity and mortality.

Its focus hinges upon a number of core elements:

1. *Balancing benefits and risks of immunization.* Changes in the immune response in pregnant women – which are thought to occur in order to allow the woman to tolerate the semi-allogeneic foetus – may interfere with the development of the specific immune response to pathogens. These immunological changes may alter the susceptibility of the woman and the foetus to certain infectious diseases and increase the risk of more serious outcomes. The immature adaptive immune systems of newborn babies and premature infants make them particularly vulnerable to morbidity and mortality due to infection. Immunization of pregnant women can protect them directly against vaccine-preventable infections, and potentially protect the foetus. It can also directly protect the foetus and infant via specific antibodies transferred from the mother during the pregnancy.

2. *Vaccination safety.* There is uncertainty about vaccination safety in pregnancy: as a matter of fact, manufacturers do not recommend it on precautionary grounds. Although, evidence related to this issue is limited, as pre-licensing clinical trials of vaccines do not usually include pregnant and breastfeeding women. Information available also provides insufficient post-licensing data, as once again, pregnant women are generally not enrolled in clinical trials. However, this has reduced the ability to make evidence-based decisions and give optimal guidance on the use of vaccines in this vulnerable population group.



3. *Risk assessment of inactivated vaccines.* Immunization with inactivated vaccines during pregnancy is not expected to be associated with any increased risk to the foetus. Inactivated vaccines with novel adjuvants, however, may need to be considered and evaluated on a case-by-case basis, as there is more limited experience related to those products

4. *Limited evidence for meningococcal vaccines in pregnancy.* Existing evidence is limited and is derived mostly from passive surveillance data for conjugated meningococcal vaccines and small studies of bi- and tetravalent polysaccharide meningococcal vaccines. The available data suggest that vaccination of pregnant women is safe and is not linked to increased risk of adverse pregnancy outcomes. Nevertheless, the low statistical power of the studies, lack of sufficient follow-up of infants, and the known limitations of passive surveillance data need to be considered. The Committee calls for further active surveillance.

5. *Obstacles to accurate risk assessment of vaccines for pregnant women and their foetuses:* Vaccine safety in pregnancy must be assessed in the context of the substantial risk of infection for the pregnant woman and her foetus in the absence of immunization: it may be challenging to distinguish typical pregnancy risks from those associated with a vaccine. While there is emerging scientific evidence showing that certain vaccines are safe for pregnant women and foetuses, policy formulation is hard to accomplish, since the knowledge base to guide decisions is still limited for some vaccines. In the context of new vaccines, the data are even more limited, because pregnant women are excluded from clinical trials and there is a lack of systematic investigation of the post-licensing experience. Theoretically, live attenuated virus vaccines given to pregnant women might be capable of crossing the placenta and infecting the foetus. As a result, most live attenuated vaccines are contraindicated or not recommended during pregnancy.

Among its recommendations, the WHO Global Advisory Committee on Vaccine Safety particularly stresses the following aspects:

- There is no evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated virus; hence, pregnancy should not preclude women from immunization with these vaccines, if medically indicated.
- Live vaccines may pose a theoretical risk to the foetus. However, there is a substantial literature describing the safety of live attenuated vaccines. No significant adverse effects on the foetus have been reported following administration of these live attenuated vaccines.
- The benefits of vaccinating pregnant women generally outweigh the potential risks, under the following conditions: 1) if they are at high risk of being exposed to a particular infection and the disease would pose a risk for the woman or her unborn child; 2) if the vaccine is unlikely to cause harm. The use of selected vaccines in pregnancy is an important aspect of prenatal care, which not only protects maternal health, but also benefits the newborn baby.

## Multiculturalism

These principles are universal and they need to be translated into specific regional, country and community contexts. They should include multicultural factors, as they are related to all countries in the world.

WHO, *Considerations regarding consent in vaccinating children and adolescents between 6 and 17 years old* (2014)

### Vulnerable groups, multiculturalism

With regard to validated vaccines and the topic of informed consent, in 2014 WHO applied a special focus about consent in vaccinating children and adolescents between 6 and 17 years old, confirming that consent is always required for vaccination: in only very few, well-described circumstances, such as life-threatening emergencies, may consent be waived.

WHO underlines that:

- Consent can be formal, verbal or implied. Formal consent can be gathered with opt-in procedure (health authorities inform the parents about the vaccination and written consent from the parent is required to opt-in, i.e. give permission for the older child/adolescent to be vaccinated) or opt-out procedure (a written form is used to allow parents to express non-consent or refusal to vaccination of their child).
- When mandatory vaccination is established in relevant provisions in law, consent may not be required. If the mandatory nature of vaccination is based on policy, or other forms of soft law, informed consent needs to be obtained as for any other vaccines. Some countries allow individuals to express non-consent (opt-out) and obtain an exemption for mandatory vaccines. This may come with certain conditions, like barring unvaccinated children from attending school during disease outbreaks.
- In a growing number of countries, the age of consent for medical interventions is set below the age of majority: this allows adolescents to provide consent for specific interventions, such as access to contraceptives or HIV testing. WHO refers that some countries have fixed the age of consent specifically to allow HPV vaccination at 12 years.
- As far as immunization programs planning to amend or introduce new consent procedures for the vaccination of older children and adolescents, besides reminding that informed consent is required for medical interventions, including vaccination, WHO encourages to:
- develop an informed consent procedure that is adapted to the local situation, to the capacity of the health system and, if relevant, school system, in a way that optimizes use of resources and public-health outcomes while respecting the rights of individuals.
- promote communication strategies and materials need to cater not only to parents but also to older children and adolescents. The level of information provided to the child should be compatible with their evolving mental capacities and with the level of their mental maturity.

The Council of Europe, *Conclusions on vaccinations as an effective tool in public health* (2014)

The document recognizes that while vaccination programs are the responsibility of individual Member States and that various vaccination schemes exist in the EU, efforts to improve vaccination coverage may also benefit from cooperation within the EU and from improved synergies with other EU policy areas, having special regard to the most vulnerable populations

identified in the different regions and individual Member States of the Union and to increasing mobility. The Council of Europe invites member states to:

- continue to improve epidemiological surveillance and evaluation of the situation concerning communicable diseases in their territories, including diseases preventable by vaccination;
- continue to improve national vaccination programs and to strengthen national capacity for carrying out evidence-based, cost-effective vaccination, including the introduction of new vaccines where considered appropriate;
- continue to develop plans and standard operating procedures in collaboration with the ECDC and the WHO to ensure a timely and effective response to vaccine-preventable diseases during outbreaks, humanitarian crises and emergencies;
- continue to develop comprehensive and coordinated approaches within vaccination programs, following the Health in All Policies approach creating synergies with broader health policies and pro-actively working with other preventive sectors;
- ensure transparency with regard to the post-marketing evaluations of vaccines and of studies on the impact of vaccination programs in order to provide reliable information for both governments, medicines regulators and manufacturers;
- actively offer appropriate vaccination to population groups considered to be at risk in terms of specific diseases and consider immunization beyond infancy and early childhood by creating vaccination programs with life-long approach;
- work with health professionals on risk communication in order to maximize their role in informed decision making;
- inform the population in order to raise its trust in vaccinations programs, using appropriate tools and communication campaigns also by engaging opinion leaders, civil society and relevant stakeholders (e.g. academia).

The European Centre for Disease Prevention and Control (ECDC), *Let's talk about prevention. Enhancing childhood vaccination uptake, Public Health Guidance*, 2016

The focus of this guide is on behaviour-related communication. Its aim is to identify ways to help healthcare providers and encourage all parents to get their children protected by vaccination, particularly those in population groups whose children are currently non and undervaccinated. The guide underlines that vaccines are safe and effective and highlights the balancing of benefits and risks for different diseases. There is no reference to informed consent form but the guidance provides a detailed information on benefits and risks of different vaccinations.

The European Centre for Disease Prevention and Control (ECDC), *Catalogue of interventions addressing Vaccine Hesitancy, Technical Report*, 2017

The report addresses the problem of vaccine hesitancy: many countries are dealing with groups of people who are reluctant or refuse recommended vaccination(s), or decide to delay some vaccines. The document contains a review of possible interventions, but there is no reference to informed consent. Nevertheless, the topic of risk is stressed and a more effective communication of the balancing of benefits and risks is highlighted.

## 3.2. Experimental and validated vaccines: EU Law

### 3.2.1. Vaccine trials as interventional studies

Vaccine trials fall within interventional research and they are not "low interventional studies" with minimal risk. The fact that such trials involve healthy subjects determines two consequences: a stringent emphasis on safety both in clinical trials and in clinical practice, and a more rigid regulation concerning informed consent. A rigorous regulatory procedure must therefore be ensured to assess quality, efficacy and safety.

Vaccine is administered to the healthy subject. Depending on the virus being tested, the volunteer may then be quarantined for a amount of time to prevent cross-infection, or spreading the virus to the general population. Within the European Union human vaccines are regulated by European Medicines Agency (EMA). All manufacturing information including tests for safety, purity, and potency for a particular product is regulated under a Good Manufacturing Practices (GMP) Directive 2003/94/EC and Regulation (EU) No. 1252/2014. The GMP requires, in general, that medicines are of consistent quality, appropriate for their intended use and that the requirements of the marketing authorisation or clinical trial authorisation are met.

### 3.2.2. Competence of vaccination policy

The EU's role in health policy is limited, because National governments are responsible for deciding how to organise their health service. The European regulatory framework does not regulate whether vaccines are mandatory or recommended, and the Member States remain free in their decision. Thus, National Health Services of most European countries have different vaccination systems, different vaccine recommendations and different schedules of vaccine administration.

The Council of the European Union, in the "Council conclusions on vaccinations as an effective tool in public health (2014/c 438/04)" recognises that vaccination programmes are under the responsibility of individual Member States and that various vaccination schemes exist in the EU. However, efforts to improve vaccination coverage must be done, especially with regard to the most vulnerable populations identified in the different regions and individual member states of the union. The council invites member states to continue to improve epidemiological surveillance and evaluation of the situation concerning communicable diseases in their territories, including diseases preventable by vaccination.

### 3.2.3. European Centre for Disease Prevention and Control (ECDC)

The Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishes a European centre for disease prevention and control. This is an

independent agency, a Community source of scientific advice, assistance and expertise from medical, scientific and epidemiological staff acting on behalf of Member States' authorities responsible for human health (article 9). Although vaccination policy is a competence of national authorities, the European Commission supports EU countries to coordinate their policies and programmes. In particular, the EU Commission encourages EU countries to ensure that children are immunised. The Council of European Union in the "Council conclusions on childhood immunization: successes and challenges of European childhood immunization and the way forward 2011/C 202/02" invites the Commission to ensure synergy between the promotion of childhood vaccination and the implementation of relevant EU legislation and policies, while respecting national competences.

#### 3.2.4. Human Papillomavirus (HPV) vaccines

Following the advice of the scientific committee of the European Medicines Agency, the EU authorised the marketing of two HPV vaccines that prevent infections with the two main strains of HPV that cause cervical cancer.

EU countries exchange information on HPV immunization using the platform called VENICE (Vaccine European New Integrated Collaboration Effort), the most important tool of primary prevention. The European Commission operates as a coordinator. The European Centre for Disease Prevention and Control funds the platform and has set up an expert group to look into introducing HPV vaccination in EU countries.

#### 3.2.5 Case law

Concerning the access to experimental treatment or drug, in the case of *Hristozov and Others v. Bulgaria* (application no. 47039/11 and 358/12), the European Court of Human Rights emphasizes a trend in European countries towards allowing the use of unauthorised medicinal products. In the case, the applicants were cancer sufferers and they complained that they had been denied access to an unauthorised experimental anti-cancer drug.

Bulgarian law stated that such permission could only be given where the drug in question had been authorised in another country. In the specific case nowhere had it been officially authorised. Consequently, the Bulgarian authorities refused permission.

The European Court of Human Rights observed a trend among European countries towards allowing, under exceptional conditions, the use of unauthorised medicine. The Court held that there had been no violation of Article 8 (right to respect for private and family life) of the European Convention on Human Rights. The Court further held that there had been no violation of Article 2 (right to life) and no violation of Article 3 (prohibition of torture and of inhuman or degrading treatment) of the Convention in that case.

In the case *Durisotto v. Italy* the European Court declared the application inadmissible under Article 8 (right to respect for private and family life) and under Article 14 (prohibition of discrimination) taken in conjunction with Article 8 of the Convention. This case concerned the

refusal by the Italian courts to authorize the applicant's daughter to undergo compassionate therapy to treat her degenerative cerebral illness (this experimental treatment known as the "Stamina" method). The therapy was undergoing clinical trials. Legislative decree established restrictive access criteria. The applicant alleged that the legislative decree in question had introduced discrimination in access to care between persons who had already begun treatment prior to the entry into force of the decree and those who were not in that situation, like his daughter.

With regard to confidentiality of personal information concerning health, in the case *Konovalova v. Russia*, the Court affirmed the violation of rights of patient recognized by Convention of Human Rights. In particular the applicant complained about the unauthorized presence of medical students during the birth of her child, alleging that she had not given written consent to being observed and had been barely conscious when told of such arrangements. More specifically, the Court held that there had been a violation of Article 8 (right to respect for private and family life) of the Convention.

### 3.3. Domestic law on vaccination

AUSTRIA

Soft law

Austrian Bioethics Commission

*Opinion of 1 June 2015 on Vaccination-Ethical Aspects.*

The Austrian Bioethics Commission conducts a thorough analysis of the main ethical issues surrounding vaccination in its Opinion of 2015, upon request of the Federal Ministry of Health.

This decision was made in an environment where the coverage of vaccination against infectious diseases is at present declining, focusing the discussion on the conflict of interests playing out between the best interest of the child, parents' rights to bring up their children in line with their own ideas and values and the issue of vaccination, as a matter of socio-political responsibility. The Commission believes it is urgent to deal with the issue, due to the fact that the fear of side effects has become greater than the fear of the specific disease in the general public.

*Protection of individuals and solidarity.* Particularly, it stresses that "vaccinations are not only of paramount importance because they protect the individual, they also have a collective

dimension (solidarity), in particular with a view to “herd immunity”, and to the pathogen-specific burden of disease, which is also reduced”.

Herd immunity only concerns pathogens transmitted from person to person, it means that even those who cannot be vaccinated are safe, as they are surrounded by vaccinated persons. This is true of everyone who cannot (yet) be vaccinated or has a contraindication to vaccination. These persons are more vulnerable to complications caused by the infection and need to be protected via an environment of vaccinated persons. In the context of herd immunity, the Austrian Bioethics Commission notes that “it leads to an advantage for those who refuse vaccination as they benefit from vaccinated persons as “free-riders”.

During the discussion around side effects or adverse events, the Commission argues that “coincidence (i.e. the simultaneity of two phenomena) is often mistaken for causality, as a high vaccination incidence coincides statistically more frequently with certain diseases. Moreover, a survey has shown that “the effects of experiencing childhood diseases” is largely considered positive by the population (e.g. benefits for children’s personality development and stronger immune systems)—in a way that does not conform with facts”.

In addition, the Commission highlights that “apart from the need for protection of vulnerable groups of persons, which can be reached by herd immunity as described above, we should not conceal the fact that there is major public interest in vaccination, in particular in view of the burden caused by the frequency or seriousness of an infectious disease and the negative impact on public life. If a large number of people falls ill simultaneously, this will jeopardize medical care for all and in an extreme case, it may even be a security risk. Broad vaccination coverage is thus a matter of national and global interest”.

*Informed consent.* For an informed decision, people need to be given guidance on the benefits of vaccination as a preventive measure in healthy persons and on potential risks such as vaccination side effects, vaccine reactions and complications. In this context, an industry-independent documentation showing the objective benefit of vaccination programs is particularly important. The existing international surveillance programs are still too heterogeneous and insufficient.

*Benefits and risks of vaccination.* It clearly states that, at present, the benefit of vaccination is clearly bigger than the vaccination risk. Deciding in favour of vaccination, even against “trivial” diseases, may thus make sense if the outcome of the risk-benefit analysis is positive, i.e. if the disease is common and the vaccination is safe. In this respect, the Commission identifies the need for improvement to reach out to the population with fact-based information.

The potential risk of being affected by or transmitting an infectious disease is different in different groups of people. With this in mind, it is recommended to take a differentiated approach to vaccination recommendations or compulsory vaccinations.

*Parental responsibility.* Regarding the children-parent relationships, the Commission stresses the fact that parents have a special responsibility as they take decisions not only for themselves but also for their children. In the context of medical care, “conflicts may on the one hand arise between the ideas of parents and the best interests of the child, and on the other hand between the personal autonomy of the parents in their role as nurturers and the public good (e.g. for the benefit of herd immunity sought by governments) under a “social contract” between the state and parents.”.

*Risks for and protection of immunocompromised patients.* Moreover, patients on immunosuppressive or immune-modulating therapy have an additional risk for infections (for instance, patients with hemato-oncological disorders and transplant patients form a group with extremely strong immunosuppression). In addition, there is considerable insecurity about the success and tolerability of vaccinations. The Austrian Bioethics Commission points out that vaccination of the personal environment or of relatives is a key protection measure.

Healthcare workers run a higher risk of contracting infections at work; hence, they also pose a risk to patients. The transmission of infections by hospital staff has been described for influenza, measles, mumps, rubella, varicella, pertussis, hepatitis A, hepatitis B and meningococcus infection.

*Reservations against vaccination.* When looking at reservations against vaccination from an ethical perspective, one must also consider the question as to whether individuals can be expected to accept the burdens and risks linked with every vaccination for the greater good of society, or more specifically, herd immunity. In fact, vaccinations serve both the protection and health-related interest of the individual and the protection of the population, which the individual in turn benefits from.

*Self-determination and societal responsibility.* From a social ethics perspective, the Commission emphasizes that “persons should orient their lives in society on the principles of solidarity, equity and the common good. Hence, the options of self-determination available due to social and medical progress must not be used arbitrarily and gratuitously; acting on one’s own responsibility remains tied to societal responsibility. This also includes a potential joint responsibility of the individual for the elimination of avoidable suffering in society, which is made possible by vaccination programs”. It therefore recalls that vaccination is also a matter of public health ethics, based on principles of solidarity, subsidiarity and relational autonomy (e.g. in this sense, our status of “being human” is also characterized by the diverse relations we have with our social and natural environment and should not be reduced to an individualistic understanding). Hence, issues such as social and global equity are important aspects of public health ethics, and vaccination plays a prominent role due to its eminent significance in this context.

Vaccinations are so important because they serve both the protection of the individual and the population at large, as the behaviour of the individual in respect of vaccination can have



an enormous impact on the health of others: it can protect or jeopardize other people. This is why some countries have made vaccination mandatory. The intervention in individual autonomy— i.e. compulsory vaccinations—is considered justified by the protection of the general public. In this sense, vaccination seems ethically indicated primarily due to the principle of non-maleficence, because refraining from vaccination (deliberately) is likely to endanger third parties. For instance, the Austrian Commission recalls the recent case of “measles in Germany, which was caused to a high extent by travelers and migratory flows. The public good of herd immunity is threatened by the position of vaccine-sceptic persons who advocate a behavior, which recognizes the benefit to the individual as the sole criterion for correct behaviour or questions the benefit of vaccination for the general public.

*Autonomy.* As a consequence, in ethical considerations regarding vaccination, the principle of autonomy plays an important role: as mentioned earlier, one aspect is parental autonomy when parents have to take decisions for their own children. The best interest of the child is the criterion that limits parental leeway for decision-making. Ideally, the interest of the general public should also be taken into account in this context.

Every decision is about a careful benefit-risk analysis based on reliable information. Parents often underestimate the risk of complications of an infectious disease, which children live through even though there would have been a vaccination against it. The Commission, therefore, emphasizes the need to strengthen health competence in the population by correct and objective information supported by evidence-based data to make the individual autonomous and enable informed decision-making.

*Beneficence and non-maleficence.* Another example regarding the potential restriction of autonomy in the interest of third parties can be found in vaccination of hospital staff. The principle of non-maleficence is a fundamental element in the professional ethics of this group. A reduction of the risk of transmitting an infectious disease and possibly endangering patients must be seen as an ethical obligation of people working in healthcare.

Health professionals thus have an ethical and moral obligation to vaccination. In this context, one can likewise expect institutions to take action so that they can protect the high-risk patients in their care.

*Criteria to restrict individual autonomy.* The question is whether compulsory vaccination can be justified as it is an intervention in the autonomy of the individual, and even one that touches physical integrity.

In view of the great importance of individual autonomy, one needs serious arguments for compulsory vaccination, with coercive measures only being the last resort if all else that intervenes in autonomy to a lesser extent fails.

In this context, the Austrian Bioethics Commission suggests setting and fulfilling a number of criteria, in order to justify a restriction of individual autonomy, under a public vaccination

program: “1. Proven efficacy: There must be scientific evidence for the impact of vaccination programs on morbidity and mortality in the target population; 2. Favourable benefit-risk ratio: The burdens and risks for participants in the prevention programs must be low whilst the decline in morbidity and mortality in the target population must be as high as possible; 3. acceptable cost-benefit ratio (in view of limited public resources, the program costs must be reasonable); 4. lowest possible degree of restrictiveness (before coercive measures are taken to curtail individual freedom, efforts must be made to increase participation by means of incentive systems and steering instruments; 5. Fair and transparent decision-making procedures”.

*Interventions in healthy individuals.* One element in the ethical debate about vaccination is that it is a population-wide intervention in healthy individuals showing no signs and symptoms. The main issue in this dilemma is that such a public health intervention comes with a certain risk, which only concerns the individual whilst it is beneficial to the population at large. This would actually violate the principle of justice. However, the counter-argument relies on the fact that it is not only a matter of individual risk versus public benefit, but it also involves individual benefit via herd immunity.

*Justice.* The Commission argues that a problem of justice only arises with those persons who do not contribute to herd immunity, but benefit from the health protection attained (which everyone participates in). This does not apply to people who cannot be vaccinated for health-related reasons (e.g. immunodeficiency) because nobody can be obliged to contribute to the common good if he is unable to.

*Recommended or compulsory vaccination.* Governmental authorities can protect herd immunity through recommended or compulsory vaccination: the document highlights the need for strong ethical reasons whenever measures significantly restricting individual autonomy are envisaged. For example, in the case of vaccination as a precondition for the admission of children to child-care facilities, which requires a careful evaluation against the backdrop of consequences (i.e. children being refused access to educational offerings and parents possibly being excluded from flexible work). In the extreme case of an imminent epidemic (pandemic) one could however even argue in favour of compulsory vaccination decreed by law.

*Risk communication.* As any other medical treatment, protective vaccination is an intervention in the physical integrity of the patient and it is only lawful if informed consent is given. Information must be provided about the actual risk of the disease, which the vaccination is against, as well as the risks and side effects of the vaccination and the vaccine protection to be expected.

Moreover, the Austrian Bioethics Commission recommends: the establishment of publicly accessible documentation on the benefit and possible side effects of vaccines, as well as on complications of a disease occurring in non-vaccinated persons—(quality of life, long-term

disability, costs and burdens caused by nursing and care services); the publication of data collected with the help of independent surveillance programs as this improves the acceptance of vaccination programs and publishing the Health Technology Assessment (HTA) on which vaccination programs and vaccination recommendations are based, in order to enhance public confidence.

Particular emphasis is placed on transparent and effective information to parents on access to no-cost vaccination schemes for children to avoid the phenomenon of vaccination refusal motivated by economic reasons, as well as on information and scientific foundations pertaining to vaccines being more strongly included in the training curricula of all health professions.

It equally calls for “the verification of the vaccination status of children when admitted to public schools / educational institutions and child-care facilities and to introduce compulsory counselling when sufficient immunization is missing”. The Commission also urgently recommends that “school vaccination programs and their implementation—in particular in respect of informed consent—be put on a reliable legal basis and that school operators and school physicians, be given legal certainty”.

*Promoting herd immunity.* In addition, it confirms that dangerous diseases transmitted from person to person, for which herd immunity is required to protect people who cannot be vaccinated, have to be tackled from an ethical perspective with the purpose of increasing vaccination coverage. The measures required to reach this goal have to be carefully selected against the backdrop of the greatest possible freedom of the individual, on the one hand, and the obligation to protect vulnerable groups of persons on the other. These measures may provide for legally compulsory vaccination under specific circumstances.

*Informed consent templates for vaccines.* The Austrian Federal Ministry for Health and Women publishes on its official website informed consent templates for vaccines, whereby it provides guidance on the patient information tailored to vaccination, which should be given together with consent forms. Specific requirements are devised with regard to necessary content, among which it is noteworthy mentioning:

- Gaining knowledge from the patient about any severe or chronic disease, recent acute illness, or allergy he/she has been suffering from
- Checking whether the patient takes regular medication and, if so, of which type
- Verifying if the patient has ever experienced discomfort or side effects after vaccination
- Becoming aware of any current pregnancy
- Providing the patient with complete, clear and understandable information on the composition of the vaccine, possible contraindications concerning the administration and side effects of the vaccine
- Giving the patient adequate information on the benefits and risks of the vaccine and making sure he/she has been granted the opportunity to discuss open questions with the vaccinating physician. However, there is no reference whatsoever to the need to adapt information to different literacy levels or diverse cultural backgrounds.

- The patient should be aware of the possible collection of electronic data and their use, as well as of the fact that the personal data could be transmitted in the course of medical care
- Additional details concerning vaccination should be conveyed to the patient if needed or directly requested by the latter, including informing him/her about the inexistence of an obligation to sign the vaccine consent form if the patient disagrees on any relevant aspects reported in the information sheet/consent form, or communicated by the vaccinating physician, or whether he/she needs further explanations.

There are no specific guidelines regarding vaccine trials, as they fall under normal ethical standards regarding drug trials.

#### Hard Law

With regard to vaccines, they fall under the regulation of normal drug trials administered to healthy subjects (see Drug Act-Arzneimittelgesetz; Medical Devices Act-Medizinproduktegesetz). Consequently, there is a strong attention on safety and information duty is heightened. Vaccine manufacturers must follow a clearly defined manufacturing process, which has to comply with international guidelines to ensure reproducibility and consistency (see soft law). Before a vaccine is allowed to be marketed in Austria, it has to undergo tests by the Austrian Federal Office for Safety in Health Care.

In the Austrian law there are no mandatory vaccinations, but there are strongly recommended vaccinations.

#### FRANCE

##### Soft law

The vaccine policy is discussed in the Report by Sandrine Hurel (*Rapport sur la politique vaccinale, janv.2016*), which focuses on the following key results:

- Adherence to vaccination cannot be taken for granted from the outset. Difficulties of adhesion differ according to the vaccines and the diseases concerned
- Need of regular information and communication (web, social networks); need of transparency and clarity of the messages and this implies a steering of the system where each of the actors of the vaccination policy finds his/her place.
- The simplification of the vaccine course would improve adherence to vaccination. Patient adherence to vaccination implies involvement of different health professionals.
- Implementation of the vaccination policy requires taking into account the issue of vaccine availability.
- Before any choice between vaccination obligations and recommendations, a public debate and a scientific consensus conference are essential

There are no specific guidelines relating to vaccine trials.

##### Hard law

Concerning vaccine trials, there are no specific regulations on the informed consent process, but they must be considered interventional research and not with minimal risk, because they are carried out on healthy subjects: therefore, informed consent regulation is stricter in that case.

With regard to vaccines in clinical practice, on June 2017 the Health Minister announced plans to move from three (diphtheria, tetanus and poliomyelitis) to eleven mandatory vaccines, in order to prevent the expansion of certain diseases. These additional eight vaccines – pertussis (whooping cough), *Haemophilus influenzae* B, hepatitis B, meningococcus C, pneumococcus, measles, rubella and mumps – were only recommended, but *Loi n° 2017-1836* makes them mandatory since 2018. Information and consent of parents is however required also if vaccines are mandatory.

## GERMANY

### Soft law

In the context of vaccination, *Recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute – 2017/2018* set out a number of requirements, among which:

- in order to comply with the immunization schedule for infants, children, adolescents and adults vaccination status should be checked regularly and brought up to date where necessary; each medical consultation should be utilised for this. Beside standard vaccination, other vaccinations may be indicated in a particular epidemiological situation or where there is a particular hazard to children, adolescents, and adults;
- It is the physician's responsibility to: provide information on the disease to be prevented and the benefits of vaccination; recommend the type and chronological order of vaccinations in each individual case, considering the indications and, where applicable, existing contraindications; determine the current health status of patients, in order to exclude acute illnesses; give behavioural recommendations following the vaccination; provide information on the commencement and duration of the protective effect, as well as to inform patients of additional protective options. The lack of a STIKO recommendation should not prevent a physician from carrying out further vaccinations when justified.
- If the indication for vaccination is not covered by a licensure valid for Germany, it encompasses an off-label use. In case of injury, off-label use has consequences for liability and compensation and places particular obligations on the physician administering the vaccine regarding documentation and the provision of information.

No further guidelines are provided for experimental vaccines and the informed consent process, as they fall under the general indications regarding clinical trials, developed by the German Permanent Working Party of Research Ethics Committees (for gender issues in clinical trials, see Deliverable D1.3).

## Hard law

There are no specific hard law regulations for informed consent in vaccine trials and they are covered by general norms on clinical trials according to Section 40 of AMG. They must be considered research with more than minimal risk, because they are carried out on healthy subjects. According to the Section 77 of AMG, the Paul Ehrlich Institute (PEI) is the authority with a special competence on vaccine trials.

As a final point, in the German law there are no mandatory vaccinations, but there are strongly recommended vaccinations.

## ITALY

### Soft law

#### Italian National Bioethics Committee (NBC)

##### *Opinion of 22 September 1995 on Vaccinations*

The Italian National Bioethics Committee has developed a thorough reflection on vaccination. In an Opinion issued in 1995, it offers a contribution to the debate on compulsory and recommended vaccines at the bioethical level, stressing their importance for individual and collective health. The obligation to vaccinate is not only grounded in the right to health, but also in the moral duty of solidarity, in line with the ethical arguments raised by the Austrian Bioethics Commission.

*Validated vaccines.* The NBC delves into the problems that are often perceived by the public opinion, with regard to the possibility of negative side effects deriving from vaccines (i.e. allergic reactions, neurological problems, infections, etc.). These difficulties require precaution and careful medical assessment whenever vaccinating minors, who are more vulnerable to adverse effects of medical treatment and incapable of deciding and taking the risks resulting from a lack of immunization.

*Benefit-risk communication.* Therefore, the Italian Committee argues for providing adequate information on the risks and benefits of vaccines, which would help to reduce the fear for harm, that may lead to an unjustified refusal of vaccines, notably in the case of minors.

*Conscientious objection and individual/collective protection.* In addition, the document brings up perplexities regarding the legitimacy of conscientious objection to compulsory vaccines, for the ensuing risk of jeopardizing the health of the individuals and the community, whenever there are no other measures to protect this individual and common good.

*Health culture.* In addition, the Committee recommends putting in place effective incentives for the promotion of a health culture, which could ultimately result in lifting the compulsory nature of vaccines, whenever the public opinion shows positive attitude towards these preventive health measures (NBC, *Opinion on Vaccinations*, 1995).

*Motion of 24 April 2015 on the importance of immunization.*

More recently, in 2015, a Motion was put forward due to the “alarming fact that the decrease in immunization coverage has brought about a considerable rise in the cases of measles worldwide. In Italy alone 1,686 cases were reported in 2014, the highest number in Europe. Even the WHO has explicitly urged Italy to take measures against this outbreak. Moreover, various cases of meningitis, some even fatal, have been recorded in different regions”. The NBC stresses its deep concern about the increasingly widespread trend to postpone or reject vaccines, which are recommended by the healthcare system and universally recognised as being effective. In this context, the NBC clarifies how “vaccines are one of the most efficient preventive measures, with a particularly positive risk/benefit ratio, having not only an important healthcare value but also an intrinsic ethical one”. Therefore, the NBC invites the Italian society to take personal and social responsibility and calls for increased efforts by the Government, the Regions and the competent institutions, so that both compulsory and recommended vaccines might achieve appropriate immunization coverage (95%).

*Safety and efficacy of vaccines.* It also emphasizes that for reasons of proven safety and efficacy, vaccines are deemed among the priority measures in the planning of healthcare coverage interventions for the population.

*Protecting vulnerable subjects.* It equally recalls that, as they are mainly intended for children, vaccines encompass an important element of equity, since it allows the protection of a category of vulnerable subjects. Moreover, the NBC states that immunization programs call for parental responsibility according to the criterion of the highest interest of the child and his/her right to be vaccinated: the consequence of any type of refusal is the risk of jeopardizing the health of third parties, due to this refusal, which raises concern for those individuals who cannot vaccinate for health reasons. It therefore notes, alongside personal interests, the solidarist and cooperative nature of vaccination (relating to herd immunity, as stressed by the Austrian Bioethics Commission).

*Informed consent.* In the context of providing appropriate information concerning vaccination, the Italian Committee strongly recommends to: implement effective advertising and information campaigns on mandatory and recommended vaccinations at national level, grounded in scientific evidence, including putting in place effective communication initiatives on internet websites, as well as detailed written and oral information at the individual level, to raise citizens’ awareness of current strategies, benefits and risks related to vaccination; carry out information and awareness campaigns for healthcare centers, family doctors, family paediatricians and the professionals involved in immunization programs, as well as school

employees. It also highlights the necessity for family doctors and pediatricians to give adequate information to their patients on how vaccination is one of the most efficient treatments, with a very positive risk/benefit ratio.

*Immunization initiatives.* Other suggestions rely on the need to respect compulsory immunization for healthcare professionals and the personnel working in schools and in other places attended by children; it also considers that “ every possible effort must be made to achieve and maintain an optimum immunization coverage through education programs for the public and the healthcare professionals, without excluding the possibility of making them compulsory in emergency cases” (NBC, *Motion. The importance of immunization*, 2015).

*Experimental vaccines.* Notwithstanding many ethical issues regarding vaccine trials are common to clinical trials in general, there are equally a set of specific problems, clearly identified by the Italian Committee:

- Some vaccines are mainly or exclusively used in paediatric population; therefore, these subjects cannot be excluded from clinical research. However, the problem of involving participants unable to express a valid consent and directly protect their own rights, becomes particularly challenging in this context; whereas if dealing with other types of drugs, this issue can be better controlled or even totally avoided.
- A number of possible side effects deriving from vaccines appear with a far low frequency rate. In order to achieve a statistically significant probability of emergence of these side effects, a very high number of research participants is required.
- Unlike other drugs which usually have limited effects over time, vaccines generate a biological response, which is likely to linger for years, and occasionally, even for a lifetime. It is thus essential not only to conduct studies with a high number of participants, but also to observe the ensuing effects for a long time.
- To verify the efficacy of vaccines, it is necessary to take into account not only their immunogenicity (which can be easily determined in the lab), but also the degree of protection they offer against natural diseases. As the latter prove to be unpredictable, they cannot be controlled by researchers; hence, it is difficult to envisage the exact timing and costs needed to complete the trial.
- Efficacy should always be determined against a specific control group, either treated with previously available vaccines, or less effective and safe ones, or with placebo. In any of the mentioned cases, however, ethical issues arise (regularly encountered also in other experimental treatments) for the participants involved in these procedures, as they may be deprived of a potential medical benefit and, therefore, this requires establishing criteria for the conditions under which it would be deemed acceptable to exclude them from the mentioned benefit.

In this context, the NBC stresses the need to overcome these problems, in order to objectively assess the efficacy of vaccines in randomized and controlled clinical studies, but also to protect the human subjects enrolled in vaccine trials, through accurate surveillance systems. Vaccine trials should always comply with the ethical standards provided for regarding general clinical trials (NBC, *Opinion on Vaccinations*, 1995).

Hard law



No specific regulations are given on vaccine trials, as they fall under the general regulation of drug trials, with special safety standards because they are usually carried out on healthy subjects with immunization purpose.

Ten vaccinations (diphtheria, tetanus, pertussis, poliomyelitis, haemophilus influenzae B, hepatitis B, measles, rubella, varicella and mumps) are mandatory for children since 2017 (Law 119/2017). Parents have to present their vaccination certificates at school and each Region must provide additional recommended vaccinations for free. Schools have to notify the local health agencies (ASL) when parents fail to present the necessary vaccination documents. Schools can only accept a physician's letter explaining the medical reasons why a child cannot be vaccinated. Fines up to five hundred euros are imposed for families that fail to vaccinate their children, but penalties must be preceded by the meeting between health authorities and families in order to inform them about the vaccination program. Nevertheless, the lack of vaccination implies the exclusion only from nursery school and kindergarten, while from primary school to high school, minors not vaccinated will normally be included in classes where the other students are vaccinated.

The decision n. 5/2018 of the Constitutional Court determined that the Law 119/2017 is compliant with the Italian Constitution and not unreasonable. It aims to protect individual and collective health on the basis of the duty of solidarity in preventing and limiting the spread of certain diseases. The Constitutional Court considered inter alia that all vaccinations made mandatory were already planned and recommended in the national vaccination plans and funded by the State. Furthermore, the shift from a strategy based on persuasion to a compulsory system is considered justified in the light of the gradual decline in vaccination coverage.

Information and consent acquisition of parents is however required also if vaccines are mandatory.

## SPAIN

### Soft law

The Committee of Bioethics of Spain has dealt with issues related to vaccination only in respect to its rejection. The Report *"Ethical and legal reasons for rejecting vaccination. Proposals for a necessary debate"* (2016) tackles the difficulties surrounding vaccination in multicultural societies.

The Committee of Bioethics calls for "respect and adequate communication with those individuals and communities that reject vaccination for religious, philosophical, or ideological reasons, explaining their responsibilities and the measures that should be taken in case of risk for public health".

## Hard law

In Spanish legislation vaccines are considered a medicinal product for human use.

The Royal Legislative Decree 1/2015, on Guarantees and Rational Use of Medicines and medical devices Law defines “medicine of human use” as “any substance or combination of substances presented for treating or preventing disease in human beings”.

Similarly, the Royal Decree 1090/2015, mean by “medicinal product for human use”: “Any substance or combination of substances presented as having properties for treating or preventing disease in human beings or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis”.

Consequently, vaccines are subject to the general rules for medicinal products for human use.

In relation to papilloma virus vaccination, a special mention should be made of the judgement handed down by the National High Court, administrative chamber, 4<sup>o</sup> section, 17 may 2017. Particularly, some considerations about risk communication are made: The duty to provide information cannot be regarded as a generic duty, and does not protect a requirement of an excessive and disproportionate information (such as information about abnormal risks). (...) The contrary would result if the information were excessive: an inhibitory effect would then take place. The information should be clear and easily understandable, and should be appropriate and proportionate to the recipient.

## UNITED KINGDOM

### Soft law

The Nuffield Council on Bioethics, *Public health, Ethical issues*, 2007

*Validated vaccines.* The Nuffield Council on Bioethics does not address the ethical issues of vaccination in an *ad hoc* document, but it refers to the topic when dealing with public health, arguing that “vaccination policies that go further than simply providing information and encouragement to take up the vaccine may be justified if they help reduce harm to others, and/or protect children and other vulnerable people. This would need to take account of the risks associated with the vaccination and the disease itself; the seriousness of the threat of disease to others; and whether a directive measure would be more effective than a voluntary one.” However, it takes a more “soft” stance, compared to Austrian and Italian documents with regard to vaccination, stating that: “after weighing up the evidence and ethical considerations”, the Council concludes that “there is not sufficient justification in the UK for

moving beyond the current voluntary system for routine childhood vaccinations.” (The Nuffield Council on Bioethics, *Public health, Ethical issues* 2007).

Briefing Note of 2016 on *Zika: ethical considerations*

*Experimental vaccines and multicultural issues.* Ethical problems surrounding the interactions between experimental vaccines and multicultural issues are mentioned in the Briefing Note of 2016 on *Zika: ethical considerations* in which the Nuffield Council stresses the fact that “the recent epidemic of the Ebola virus disease highlighted the critical importance of sensitivity to local conditions on the part of international researchers, and the creation of trusting relationships with local communities. Appropriate study design needs to take into account both the necessary scientific rigour and an understanding of what is locally acceptable, particularly in the absence of any effective standard treatments and widespread anxiety about the consequences of infection” (The Nuffield Council on Bioethics, 2016). It therefore suggests envisaging early discussion and collaboration with local research ethics committees, in order to maximise the chance of prompt consideration of innovative trial designs. Where necessary, local research ethics committees should be able to rely on international support. This could encompass local committees commissioning preparatory work from other countries or requesting advice or personnel to foster local capacity.

UK General Medical Council, *Good Medical Practice*, 2013

*Challenge studies.* In the context of experimentation with vaccines, highly sensitive ethical issues can arise from the so-called “challenge studies”, since they concern intentionally infecting healthy people in order to investigate diseases and their treatments. This type of research is common in medical research, especially in the development of vaccines; although, many national guidelines do not specifically deal with human challenge studies.

In this regard, the UK General Medical Council guidelines for doctors state: “...in non-therapeutic research, you must keep the foreseeable risks to participants as low as possible and the potential benefits from the development of treatments and furthering of knowledge must far outweigh any such risks”. This guidance, besides arguing that there is to some extent a balance between risk of harm to the participants and the expected value of the research, makes the important additional point that the risks should be kept as low as possible. In other words, even if the risks of harm were within acceptable limits, and, of course, the participant had given valid consent to take part, the research may be in breach of the guidelines if it could have been carried out more safely (General Medical Council, *Good Medical Practice*, 2013).

Some guidelines make clear distinctions between therapeutic and non-therapeutic research and between patients as participants and healthy volunteers. In this context, only the case of healthy volunteers is taken into account, since these are the usual participants in “challenge studies”. The question is what degree of risk or harm is acceptable for fully informed healthy adult volunteers.

The Royal College of Physicians, *Guidelines on the practice of ethics committees in medical research involving human subjects*, 1996, 2007

*Minimal risk.* The Royal College of Physicians (RCP) guidelines have been the most explicit on this point by including a concept that is often used in this context, that of minimal risk of harm, or minimal harm. The second edition of these guidelines (1990) devised a key distinction between two meanings of minimal harm. On the one hand, harm can be minimal in the sense that, although quite likely, or even certain, it is not very great (i.e. the headache that can follow a lumbar puncture might be an example of minimal harm). The second meaning of minimal harm is where there is a very low chance of serious harm. The second edition of the RCP guidelines underline, in the context of minimal risk:

This second meaning is “where there is a very remote chance of serious injury or death” (i.e. this second risk to the healthy volunteer is deemed to be comparable, for instance, to that of flying as passenger in a scheduled aircraft). Although, according to these guidelines, “there are some situations, such as the treatment of serious disease, where it is ethical for research studies to involve more than minimal risk. These would never involve healthy volunteers”.

In the third edition of the guidelines, the Royal College no longer refers to airplane flights and elaborates the meaning of minimal risk in the following way:

“Minimal risk could include everyday risks such as travelling on public transport or a private car (the latter having considerably higher risk) but would not include travel by pedal motorcycle; Minimal risk is where the chance of serious injury or death is very remote and may be ignored”.

The guidelines go on to state: “benefit may be weighed against risk in two different ways. First and most obviously, the patient may benefit. This is typified in a therapeutic trial where at least one of the treatments offered may be beneficial to the patient. Second, society rather than the individual may benefit. In such situations, however large the benefit, to expose a participant to anything more than minimal risk needs very careful consideration and would rarely be ethical”.

Although, the Royal College has attempted to tackle the question of how much risk of serious harm a healthy volunteer can be exposed to, it is not clear what degree is acceptable, other than that the risk has to be very low. The guidelines are, nevertheless, interesting in making clear that the risk that a participant can take in participating in medical research must be less than a risk that many of us take in normal life (Royal College of Physicians, *Guidelines on the practice of ethics committees in medical research involving human subjects*, 1996, 2007).

For a discussion of gender issues in clinical research, see D1.3.

Hard law

There are no specific regulations in the UK legal system on experimental vaccines and they are covered by general norms on clinical trials. They must be considered research with more than minimal risk, because they are carried out on healthy subjects and informed consent regulation is stricter in that case.

No mandatory vaccines are provided for by the law, but there are recommended vaccinations.

### 3.4 Illustrative cases: Meningitis, HPV, RSV

#### 3.4.1 Meningitis

WHO, *Position paper on Meningococcal Vaccine* (2015)

WHO emphasizes the importance of completing mass vaccination campaigns in individuals aged 1–29 years in all countries in the African meningitis belt, and the need to conduct high quality surveillance and vaccination programme evaluation in those countries. The 2015 recommendations are additional to those in the 2011 position paper.

WHO recommends that countries completing mass vaccination campaigns introduce meningococcal A conjugate vaccine into the routine childhood immunization programme within 1–5 years.

EMA, *European Medicines Agency recommends approval of first vaccine for meningitis B*, 2012

European Medicines Agency recommends approval of first vaccine for meningitis B Vaccine to provide broad coverage against meningococcal group B infections: in 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a marketing authorisation for Bexsero, a new vaccine intended for the immunization of individuals over two months of age against invasive meningococcal disease caused by *Neisseria meningitis* group B. Before, there was no authorised vaccine available in the European Union (EU) for bacterial meningitis caused by *Neisseria meningitis* group B.

European Centre for Disease Prevention and Control, *Expert opinion on the introduction of the meningococcal B (4CMenB) vaccine in the EU/EEA*, 2017

This expert opinion document aims to support national decision-making by summarising the considerations and concerns of some EU/EEA Countries about the introduction of the 4CMenB vaccine into their national immunisation programmes. It also presents options on how to introduce the vaccine. There is no reference to the topic of informed consent.

#### 3.4.2 Human Papilloma Virus (HPV)

WHO, *Position paper on HPV Vaccine* (2017)

WHO position paper has received an up-to-date in 2017 (the former version was of 2014). At the international level as well as on the European one references to the topic of informed consent regarding HPV vaccine are low and they should be implemented, in particular

because in this case the recommended target is a vulnerable group (women), generally from 9 to 15 years old.

WHO recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and reiterates its recommendation that HPV vaccines should be included in national immunization programmes, provided that: prevention of cervical cancer and/or other HPV-related diseases constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered.

2017 WHO position paper replaces the 2014's one on vaccines against diseases caused by HPV. It focuses primarily on the prevention of cervical cancer, but also considers the broader spectrum of cancers and other diseases preventable by HPV vaccination. New recommendations are proposed regarding vaccination strategies targeting girls only or both girls and boys, and vaccination of multiple birth cohorts.

HPV vaccines should be introduced as part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV, with these clarifications:

- this strategy should include education about reducing behaviours that increase the risk of acquiring HPV infection, training of health workers and information to women about screening, diagnosis and treatment of precancerous lesions and cancer. The strategy should also include increased access to quality screening and treatment services and to treatment of invasive cancers and palliative care.
- the introduction of HPV vaccine should not undermine or divert funding from developing or maintaining effective screening programmes for cervical cancer. HPV vaccination is a primary prevention tool and does not eliminate the need for screening later in life, since the vaccines do not protect against all high risk HPV types.
- the introduction of HPV vaccination should not be deferred because other relevant interventions cannot be implemented at the same time.

WHO, recommends that all countries proceed with nationwide introduction of HPV vaccination.

## Gender

For the prevention of cervical cancer, the WHO-recommended target age group for HPV vaccination is girls aged 9–14 years, prior to becoming sexually active. This is because HPV vaccines are most efficacious in those who have not previously been exposed to the virus. Vaccination strategies should initially prioritize high coverage in the WHO-recommended primary target population of young females 9–14 years of age. Vaccination of secondary target populations of older adolescent females or young women is recommended only if this is feasible, affordable, cost effective, and does not divert resources from vaccinating the primary target population or from effective cervical cancer screening programmes.

HPV vaccination of males is not recommended as a priority, especially in resource-constrained settings, as the available evidence indicates that the first priority should be for cervical cancer reduction by timely vaccination of young females and high coverage with each dose.

#### Vulnerable groups

The safety and efficacy of the HPV vaccines in children younger than 9 years have not yet been established. In the absence of well-controlled studies in pregnant women, vaccination with HPV vaccine is not recommended in pregnancy as a precautionary measure.

HPV vaccines have excellent safety and efficacy profiles.

According to the WHO, a policy regarding consent needs to be in place in HPV vaccination, in particular informed consent process for routine immunization services and vaccines delivered during campaigns, and the applicability of these policies for HPV vaccines delivered to girls aged 6 to 14 years. The above mentioned document “Obtaining consent in vaccinating children and adolescents between 6 and 17 years old” (2014) is also important in this respect because the target population group for HPV vaccine may present for vaccination without an accompanying parent or legal guardian.

WHO, *Summary of Key Points of the WHO Position Paper on Vaccines against Human Papillomavirus (HPV)*, 2017

#### Vulnerable groups

The document contains some key points regarding vulnerable groups:

- HPV vaccination of pregnant women should be avoided due to lack of data, though no adverse effects in mother or offspring have been observed;
- if a young female becomes pregnant after initiating the vaccination series, the remaining dose(s) should be delayed until after the pregnancy is completed;
- breastfeeding is not a contraindication for HPV vaccination.

WHO, *Guidelines for the introduction of HPV vaccine into National Immunization Programs* (October 2016)

The document contains useful references to the topic of consent in HPV vaccination. In particular, the consent process needs to be carefully planned and implemented, considering this elements:

- specific policies and procedures for obtaining individual informed consent for HPV vaccines will need to consider local infrastructure and resources. For HPV vaccines, some countries have found that the introduction of a new or different consent procedure has led to suspicion that the HPV vaccine is experimental or risky;
- the form of consent is the above mentioned WHO document about the obtaining of consent in children from 6 to 16 years (written, verbal or implied consent);
- the authorization of local or national school authorities for the intervention (vaccination) to take place does not imply informed consent by the individuals in that school or community. In a legal sense, school



or local welfare or other community authorities do not have the capacity to consent to medical interventions on behalf of the children in their care. Exceptions, stipulated in local laws and regulations, may exist in defined, special situations.

- when mandatory vaccination is established in relevant provisions in law, consent may not be required. If the mandatory nature of vaccination is based on policy, or other forms of soft law, informed consent needs to be obtained. Some countries allow individuals to express non-consent (opt-out) and obtain an exemption for mandatory vaccines.
- for childhood vaccination, parental consent can be implied when a parent voluntarily brings the child to be vaccinated at a health clinic. However, older girls may not be accompanied by parents at the time of HPV vaccination, regardless of location. In these situations, implicit parental consent cannot be as easily assumed, and explicit written or verbal consent may require additional steps. Any explicit consenting or authorization process needs to be accounted for in the microplan and timeline established for HPV vaccine introduction.
- regardless of a country's informed consent policy, information and education to girls, their parents, teachers and the community should be given to allow understanding of the benefits and risks of HPV vaccination and to ensure acceptance.

On the EU level, there is no reference to the obtaining of consent in HPV immunization program.

ECDC (European Centre for Disease Centre and Control), *Guidance for the introduction of HPV vaccine in European Countries* (2008)

The document reports that authorities in several EU countries have already decided to include HPV vaccine in routine immunization programmes. The primary target group in all of these countries is girls of an age before sexual activity becomes common. Therapeutic vaccines may be developed.

In the 2012 update, ECDC Guidance underlines:

- since 2008, HPV vaccination programs have been implemented in most EU countries. By May 2012, 19 out of 29 countries in the EU (including Norway and Iceland) had implemented routine HPV vaccination programs, and 10 countries had also introduced catch-up programs;
- The HPV vaccines currently in use for girls are generally safe, well tolerated and highly efficacious in the prevention of persistent infection, cervical cancer and cancerous and precancerous lesions related to the vaccine-HPV serotypes.

As far as immunization is concerned:

- school-based immunization is likely to be the lowest-cost option for delivery of HPV vaccines to pre-adolescent girls. However, local issues, such as whether there are school-based health services, funding arrangements for vaccine purchase and administration and obtaining parental consent may affect the feasibility of this approach.
- Clinic or practice-based immunization is a universally available, additional or alternative option for HPV vaccine delivery. This may be more expensive than school-based immunization and monitoring vaccine uptake may be more difficult. Sexual and reproductive health and other medical clinics provided specifically for women may be important sites for immunization. However, girls may not visit them before the onset of sexual activity and so they are likely to be useful mainly for catch-up programs targeting older adolescents and women. Other settings may exist for provision of HPV vaccine to girls in

'hard to reach' communities and for opportunistic immunization when girls visit medical services for other reasons.

- Existing immunization programs for adolescents and other ongoing health promotion activities should be taken into account when planning delivery strategies for HPV vaccine.

### 3.4.3 Respiratory Syncytial Virus (RSV)

WHO, RSV Vaccine Research and Development Technology Roadmap (2017) There is no WHO position paper on RSV, but a 2017 (focusing on activities for development, testing, licensure and global use of RSV vaccines, with a specific focus on the medical need for young children in low- and middle- income countries).

EMA, *Guideline on the clinical evaluation of medicinal products, indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease*, 2017

#### Vulnerable groups

The Guideline addresses clinical development programmes for medicinal products intended for the treatment of disease due to respiratory syncytial virus (RSV). The guideline also addresses vaccination of pregnant women with the aim of preventing RSV disease in their infants. It covers the clinical development of vaccines for the prevention of RSV disease and direct acting antiviral agents for the treatment of RSV disease. The focus is on the assessment of safety and efficacy in populations most likely to develop RSV lower respiratory tract infection and severe RSV disease, including (newborn) infants and older children predisposed to develop severe RSV disease and the elderly. The draft guideline proposes some considerations on nonclinical investigations of efficacy and risk of vaccine-associated enhanced disease to support clinical trials with preventive or therapeutic products directed at RSV.

There are no references to the issue of informed consent.

## 4. Recommendations on informed consent in translational/clinical research and vaccination

Not all ethical requirements for (standard) clinical trials will be developed, but only specific elements relating to translational research, with a special consideration of informed consent and vulnerable populations:

### Risk communication

1. Given the unavoidable uncertainty of translational research and the different degree of risk involved in specific clinical research types and phases, risk communication is of paramount importance: a careful communication of risks (and their uncertainty) and adequate and effective verification of the understanding of all risks at stake should be ensured in the relationship between researchers and patients.
2. The circularity of information needs to be fostered from the physician to the patient, and from the patient to the physician (in a symmetrical way with respect to the circularity of translational research, from bench to bedside and backwards). The fully conscious participation of the patient should be ensured, with specific improvement of an active and not only passive participation (the patient should not only receive information from the physician, but also give information to the physician). The informed consent should refer explicitly to the active involvement of the patient in the information process.
3. The informed consent should entail an explicit reference to the specificity of translational research (compared to other kinds of research) and, above all, to the blurred boundaries between research and therapy in translational research, to the potential innovation of research and to the possibility of acceleration of research. The informed consent should explain to the patient that the possible acceleration/innovation of research does not mean a decrease in attention to safety issues.
4. Criteria to define, assess and calculate risks and burdens should be specifically introduced in the informed consent, clearly explaining the difference between high and minimum risks.
5. Before participating in first-in-human clinical trials, human subjects must be explicitly and clearly informed about the uncertainty of the expected benefits and the potential risks deriving from unpredictable toxic effects. Researchers should also explain that starting the trial is the only way to overcome this scientific uncertainty and to possibly find a therapy.
6. In case of minimal risk, formal procedures to obtain informed consent can be simplified, but the duty of information should not be reduced.

### Benefit communication

7. The informed consent process for research participants should include and clearly specify possible direct benefits to the individual and indirect health benefits for the individual/community, when existing.

### Information and verification tools

8. Specific tools should be adopted to concretely evaluate the level of understanding of the information about risk communication.

### Innovative therapies

9. Informed consent is essential when a patient is called upon to decide whether or not to start innovative therapies, which should always be subject to ethical oversight. Not only do physicians and researchers have the duty to provide clear information concerning the experimental treatment, but also to make sure that the patients are adequately aware of the potential conflict between therapeutic purposes and the goal of gaining new knowledge.
10. Physicians and researchers should make sure that patients have fully understood all potential benefits and risks involved in using innovative therapies, in order to overcome possible therapeutic misconception.
11. It is important to avoid research misconduct and conflict of interests involving sponsors and those who administer innovative therapies and no pressure must be exerted by physicians and researchers, for professional reasons, on emotionally vulnerable individuals affected by severe, rare or life-threatening disease. The informed consent should be accompanied by a declaration of absence of conflict of interest and integrity of research.

### Risks and burden minimisation

12. Criteria for risk and burden minimisation should apply to all population groups, including those who are able to give consent. In any case, researchers should prove and the competent research ethics committee should evaluate whether or not a research project fulfils the established criteria, in order to provide guarantees of high-quality clinical research, which is crucial for the development of innovative therapies.
13. In phase I trials in cancerology, patients should be adequately informed of their right to receive palliative care, in order to preserve their quality of life: the rationale of such trials entails a risk that quality of life can be undermined by a series of side effects to which effective remedy must be provided.

## Healthy subjects

14. In the case of healthy subjects taking part in a translational/clinical research, informed consent must enable the subject to understand that early stages of clinical trials do not primarily have a therapeutic objective, since the core focus remains on safety. Risk communication must be deepened and carefully assessed.
15. In case of healthy volunteers involved in research on non-therapeutic treatments (such as experimental vaccines), the informed consent should explicitly refer to the absence of undue inducement or compensation, which may lead them to underestimate the risks linked to participation.

## Emergencies: conditions that justify the presumed informed consent

16. Clinical trials in emergency situations, whenever the patient is incapable of providing his/her valid informed consent, and in the absence of a legal representative, should be deemed acceptable under strict conditions: the approval of a protocol (based on strong experimental evidence) by an independent ethics committee, composed of physicians and other health care professionals working in the field, legal experts, patient rights' representatives and bioethicists; the ascertainment of any possible wish opposing the experimentation previously expressed by the patient; the request for a "deferred consent" by the patient in case he/she regains capacity or by the legal representative, should the incapacity continue; the publication of trial results (specifying positive or negative findings) to avoid unnecessary duplications.

## Gender, age, and multiculturalism

17. Given the specific ethical issues which can be identified in translational research, notably in terms of safety, ad hoc guidelines on best practices and standards orienting the informed consent process should be elaborated in this context, with a strong focus on possible interactions between gender, age, and multicultural issues, which is often missing.
18. As a general principle, adequate and clear information must be given to the subjects involved in clinical research, making sure that it has been understood. Thus, translation and cultural mediation may be used as means to fulfil those ethical and legal requirements.

## Vaccination

19. For an informed decision, people should receive guidance on the benefits of vaccination, as a preventive measure in healthy persons, and on potential risks, such as vaccination side effects, reactions and complications, while taking into account the potential effects of vaccination on the specific health condition of patients.

20. The informed consent should make an explicit reference to the meaning of 'herd immunity' and to the personal responsibility towards one's own health and the community.
21. There is need of specific informed consent in case of immunocompromised patients, specifying the additional risk for infections and that vaccination of the personal environment or of relatives is a key protection measure, as well as a moral obligation to avoid health risks for these particularly vulnerable individuals.
22. Specific information to parents is necessary, since they often underestimate the risk of complications of an infectious disease, which children live through without vaccinating against it; information should be accompanied by promotion and improvement of health culture in the population, through accurate and scientifically rigorous information, supported by evidence-based data, to facilitate autonomous and informed decision-making.
23. Pregnant women should be adequately informed of the importance to vaccinate, in order to protect their foetus, but only when the benefits of vaccination significantly outweigh the potential risks; therefore, under specific conditions, which require careful consideration: 1) if these women are at high risk of being exposed to an infectious disease, that is most likely to pose a risk for the woman or her unborn child; 2) if there are reliable evidence-based reasons supporting the conviction that the vaccine will not cause harm to the pregnant woman and to her foetus.
24. The informed consent in the context of vaccine trials, in the so-called "challenge studies", should include an explicit mention of the intentional infecting of healthy people, in order to investigate diseases and the ways to eradicate them. In non-therapeutic research, one must keep the foreseeable risks to participants as low as possible and the potential benefits from disease prevention and development of knowledge must far outweigh any such risk.

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