Special issue

Informed Consent in Translational/Clinical Research. Ethical Issues According to International Guidelines

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ABSTRACT: In translational research, the emphasis on advancements in scientific knowledge could prevail over the protection and the best interest of those who participate in the research; in particular, the duty of safety for human subjects could become far more challenging when moving from preclinical research to first-in-human trials, because of uncertainty, as preclinical research can fail to predict the risks for humans, and of risk, which could result in a greater than minimal risk, because of the acceleration of research in the shift from bench to bedside. The article discusses from an ethical point of view specific issues which informed consent in translational research should take into account.

KEYWORDS: Translational/clinical research; ethics; informed consent; safety; risk

SUMMARY: 1. Ethical issues in translational research – 2. Translational research: international documents and guidelines – 3. Informed consent in translational research – 4. Analogies and differences between innovative therapies and translational research – 5. The primary duty of safety for research participants in the leap from bench to bedside.

1. Ethical issues in translational research

In the medical field, the objective of translational research is, first of all, to transfer scientific knowledge from laboratory and pre-clinical research to clinical research on human subjects and to translate knowledge and advances generated in biomedical research into positive impacts on human health[1].

Basic research aims to generate knowledge but perhaps may not be immediately relevant for practical applications in patient care; translational/clinical research is described as research protocols involving patients. "The whole spectrum of research is essential, from basic, through translational to

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[1] "A growing attention of the scientific community, of the governments and of the public opinion is today focused on the need of promoting translational research for health by initiatives instrumental for allowing the efficient transfer of the scientific discoveries into feasible preventive and therapeutic strategies for diseases at high socio-economic impact and relevance for the national health plans" (ISTITUTO SUPERIORE DI SANITÀ, *Infrastructures for Translational Research on Health and the Role of Istituto Superiore di Sanità*, November 2014, *Preface*, available at http://old.iss.it/binary/iatr/cont/Opuscolo_IR_2014.pdf, last visited 26/04/2019.

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patient-oriented research and back again. One part is ineffective without the other"[2]. For this reason, it is difficult to set clear boundaries between basic research and translational/clinical research. Nevertheless, the process of translation of knowledge can be defined as "the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public – from diagnostics and therapeutics to medical procedures and behavioural changes. Translational science is the field of investigation focused on the understanding the scientific and operational principles underlying each step of the translational process"[3]. *The European Society of Translational Medicine*[4] defines translational medicine as "an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and the community. The goal of translational medicine is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies"[5]. In this perspective, translational research 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. The concept of a "two-way road" or "two-way bridge" was developed when the overall scope of biomedical research – scientific knowledge – became closer to the help that clinical scientist engineers could give to health care through emerging technologies, taking advantage also of the increase of funding in this area[6].

The increasing development of translational research with human subjects[7] poses new challenges to the fulfilment of ethical standards for the protection of the human subjects involved, particularly in

[2] EUROPEAN SCIENCE FOUNDATION, *Implementation of Medical Research in Clinical Practice*, 2011, n. 5, available at http://archives.esf.org/fileadmin/Public_documents/Publications/spb45_ImplMedRes_ClinPract.pdf, last visited April 26th, 2019. This document explicitly deals with translational research and particularly with the difficulty to set clear boundaries between basic research and clinical research. In addition, in Annex 2 (Glossary), the document defines translational research as "the conversion of basic research advances into products that can be tested on humans" and in Annex 3 (Future Outlook: Emerging Innovative Approaches for Effective Integration of Medical Research in Clinical Practice) as "the multidisciplinary research necessary to advance preclinical or basic science findings to clinical and population health applications is often named as translation research".

[3] NATIONAL INSTITUTE OF HEALTH, *Translational Science Spectrum*, 2015, https://ncats.nih.gov/files/translation-factsheet.pdf, last visited April 8th, 2019.

[4] The European Society of Translational Medicine (EUSTM) is a global non-profit and neutral society whose principal objective is to enhance world-wide health care through the specific development and eventual clinical implementation and exploitation of Translational Medicine-based approaches, resources and expertise (The European Society for Translational Medicine, https://eutranslationalmedicine.org/, last visited April 8th, 2019).

[5] J. SHAHZAD ET. AL., *Translational Medicine definition by the European Society for Translational Medicine*, in New Horizons in Translational Medicine 2 (2015), p. 88.

[6] J. SHAHZAD ET. AL., *Translational Medicine definition by the European Society for Translational Medicine*, cit., p. 87. Also the NIH defined translational research as a two-way road "Although sometimes referred to as bench-to-bedside research, translational research really is a two-way street. Basic research scientists provide clinicians with new tools for use with 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 endeavour, as they provide the feedback necessary to ensure the practicality of interventions" (THE NATIONAL INSTITUTE OF HEALTH, *Biennial Report of the Director*, Fiscal Years 2006-2007, available at https://report.nih.gov/biennialreport0607/, last visited April 8th, 2019).

[7] 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

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terms of risk. Every research which aims at innovation entails uncertainties and risks[8], which may be totally or partially unpredictable. 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, accelerated also by emerging technologies[9] needs greater precaution and caution to ensure that the timelines of procedures do not override the necessary protection and risk/benefit proportionality[10], which must be guaranteed to research participants.

In addition to the ethical issues in common with biomedical research in general – for example identifying principles and values of the research, the responsibilities of the various stakeholders, and an ethical oversight –, in the shift *from bench to bedside,* there are some specific problems related to the case of "first-in-man trials", where "the focus of research must always be on patients' interest. Therefore, the main problems are connected to the safety of those who participate in the research and to balance risks and benefits"[11]. The transfer *from bench to bedside* is a primary concern in translational research; however, 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[12]. In particular, when risks are too high compared to the benefits than can be reached (with a non-proportionality of

new therapies or medical procedures (see CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, *Preface*, available at https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, last visited April 8th, 2019).

[8] In medical practice and medical research most of interventions involve risks and burdens, which must always be assessed before conducting a study involving humans (World Medical Association, *Declaration of Helsinki*, 1964 last version 2013, art. 16-17, available at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/, last visited April 8th, 2019). Risks are ethically justified for the scientific and social value of research and should always be carefully balanced (see CIOMS, *Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 4, *Potential individual benefits and risks of research*, which recommends: " […] Before inviting potential participants to join a study, the researcher, sponsor and the research ethics committee must ensure that risks to participants are minimized and appropriately balanced in relation to the prospect of potential individual benefit and the social and scientific value of the research".

[9] For an ethical overview of emerging technologies in scientific research, see L. Palazzani, *Innovation in scientific research and emerging technologies: a challenge to ethics and governance*, Cham (Switzerland), 2019, pp. 157.

[10] Risk/benefit proportionality is a general ethical requirement for clinical trials. See CIOMS, *Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 4, *Potential individual benefits and risks of research*: "For or research interventions or procedure that offer no potential individual benefits to participants, the risks must be minimized and appropriate in relation to the social and scientific value of knowledge to be gained (expected benefits to society from the generalizable knowledge)".

[11] See C. Petrini, *From bench to bedside and to health policies: ethics in translational research*, in Clinical Terapeutics, 162 (1), 2011, pp. 51-59, p. 52. See also C. Petrini, *Ethical Issues in Translational Research*, in *Perspectives in Biology and Medicine* 53 (4), 2010, pp. 517-533.

[12] There is a need to balance freedom of scientific research with respect for human dignity and human rights: "the risk in human research is that the emphasis on advancements in scientific knowledge might prevail over the protection of and the best interests of those who participate in research" (See C. Petrini, *From bench to bedside and to health policies: ethics in translational research*, cit., pp. 52-53).

risks/benefits), researchers have the responsibility to stop the study (even if research participants/patients request to continue). Furthermore, this can become particularly problematic when vulnerable population groups are enrolled in research (i.e. minors or fertile women). Even if the general ethical principle state that vulnerable individuals should be excluded from greater-than-minimal risk clinical trials[13], some documents stress the need to include them in research, so they can reap the benefits of their participation[14].

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[15]). 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. 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[16].

While translational research does not need to investigate completely novel routes to ethical reviews, it does perhaps call for the application of logic to identify the right procedures by applying the basic ethical values of research with human subjects to the specific context[17].

2. Translational research: international documents and guidelines

Within international recommendations and guidelines concerning biomedical and clinical research, some international documents address issues related to translational research. These documents

[13] See WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki*, 1964 (last version 2013), cit., art. 20 ("Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research").

[14] In the latest version of CIOMS Guidelines, 2016, cit., we can read that "special protections are warranted to pregnant and breastfeeding women to ensure that their rights and interested are protected", when they are involved in scientific research (see J.J. VAN DELDEN, R. VAN DER GRAAF, *Revised CIOMS International Ethical Guidelines for Health-Related Research Involving Humans*, in *Journal of the American Medical Association*, 317(2), 2017, pp. 135-136.

[15] The case of therapeutic misconception – when the envisaged benefits of undergoing a clinical trial are overestimated and/or assimilated with a medical treatment – will be later discussed in this contribution (see par. 3).

[16] We will further deal with this issue in par. 5.

[17] C. PETRINI, *From bench to bedside and to health policies (and back): ethics in translational research*, in *Annali dell'Istituto Superiore di Sanità*, 50 (1), 2014, pp. 62-66, p. 66.

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underline mainly the three aspects: the importance of filling up the so-called "know-do gap"[18] between the laboratory/scientific side and the healthcare one; the blurred boundaries inside scientific research in itself, as the difference between basic research, clinical research and translational research has not clear boundaries; last but not least, the stress on safety for research participants, in particular in the case of the first testing of a drug on humans and when dealing with healthy volunteers, as it is in the case of experimental vaccines[19].

In the context of global health, the WHO in 2004 addressed translational research defining it in relation to the process of linking scientific knowledge to health care and in particular to public health. Translational research is there defined as "the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease"[20]. According to the document, 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. In this perspective, research is essential, but not sufficient, to decide which policies and practices to promote and implement. The notion of "knowledge for better health"[21] involves a continuous cycle of research, application and evaluation, and learning from that experience: 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. Improving health indeed requires the application of research, namely of biomedical sciences: in the "know-do gap" recalled by UNESCO International Bioethics Committee in 2010[22], there is the space of translational research, trying to join research and clinics and needing ethics guidelines for this scope and promoting the double-way road from research to clinical practice and backwards. *The European Research Infrastructure in Medicine* (EATRIS)[23] promotes translational research, trying to join the different worlds represented by ac-

[18] UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report on Social Responsibility and Health* (2010), n. 50, available at https://unesdoc.unesco.org/ark:/48223/pf0000187899, last visited 08/04/2019.

[19] We will further deal with this aspect in par. 5.

[20] WHO, *World Report on Knowledge for Better Health* (2004), *Glossary of Terms*, p. 157, available at https://www.who.int/rpc/meetings/en/world_report_on_knowledge_for_better_health2.pdf, last visited 26/04/2019. Chapter 1 of the Report ("Learning to improve health") and chapter 4 ("Linking research to action") are particularly important for a general orientation about translational research.

[21] WHO, *World Report on Knowledge for Better Health*, cit., p. XV.

[22] From the perspective of Global Health Care, the International Bioethics Committee in 2010 highlighted 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" (UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report on Social Responsibility and Health*, 2010, cit., n. 50).

[23] Encouraged by the European Commission, in Europe EATRIS is one of the most important initiatives in order to promote translational research. 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

ademia and scientific researchers, industry and governments, in order to foster the transfer of scientific discoveries into feasible preventive and therapeutic strategies for disease at high socio-economic impact and relevant for national health plans[24]. EATRIS boosts the aim of accelerating innovation in life science and in the health care sector, by providing academia as well as industry easy and broad access to preclinical and clinical translational research infrastructure, to facilitate the development of new products and services in medicine along the entire research and development process up to the clinic[25]. It should be added that bridging the gap between scientific knowledge and development in the healthcare sector may imply different form of participation and the corresponding ethical requirements must be always fulfilled[26].

Concerning translational research insofar as it is defined in international and institutional documents, boundaries among the phases of research are blurred. The National Institute of Health (NIH)[27] consider together clinical and translational research, because the two areas overlap, with translational efforts often focusing on overcoming barriers that may impede the progress of clinical research. The 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"[28]. Following this definition, NIH considers translational research as divided in two stages: the first is aapplying discoveries generated during research in the laboratory to the development of studies in humans. Such preclini-

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the prevention, diagnosis and treatment of diseases of particular public health significance and economic impact (www.eatris.eu, last visited April 26th, 2019; see also the presentation of EATRIS in ISTITUTO SUPERIORE DI SANITÀ, *Infrastructures for Translational Research on Health and the Role of Istituto Superiore di Sanità*, November 2014, cit., p. 6).

[24] "The coherent promotion of translational research for health represents a transnational primary objective for the scientific progress, for the economy and for the improvement of the quality/costs ratio of the national health service. In this context, the European Commission (EC) fostered the development of some Infrastructures for Biomedical Research, as instruments to speed up the transfer of scientific discoveries into innovation and measures for public health" (ISTITUTO SUPERIORE DI SANITÀ, *Infrastructures for Translational Research on Health and the Role of Istituto Superiore di Sanità*, cit., Preface).

[25] G. VAN DONGEN, A. USSI, F. DE MAN, G. MIGLIACCIO, E*ATRIS. A European initiative to boost translational biomedical research*, in *American Journal of Nuclear Medicine and Molecular Imaging*, 3 (2), 2013, pp. 166-174.

[26] The European Group on Ethics and New Technologies recommends that special attention should be given also to the new forms of engagement of the community and of citizen in science and in biomedical research, from an ethical point of view. 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", EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE), *The ethical implications of new health technologies and citizen participation. Opinion n. 29*, 2015, available at http://ec.europa.eu/research/ege/pdf/opinion-29_ege.pdf, last visited 26/04/2019, p. 25.

[27] NATIONAL INSTITUTE OF HEALTH, *Biennial Report of the Director*, 2006-2007, cit.

[28] NATIONAL INSTITUTE OF HEALTH, *Definitions under Subsection 1-Research Objectives*, Institutional Clinical and Translational Science Award, 2007, available at https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-007.html, last visited 08/04/2019.

cal translational investigations are often carried out using animal models, cell cultures, samples of human or animal cells, or experimental systems; the second, 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[29], 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. Also *The European Science Foundation* (ESF) explicitly deals with translational research and particularly with the difficulty to set clear boundaries between basic research and clinical research[30]. In addition, the EGE Statement on gene editing[31], 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"[32]. Moreover, in another part of the statement, the European Group on Ethics 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"[33].

Concerning safety of research participants, CIOMS guidelines heighten the importance of translational research, implementing relations between basic research advances and their use, in order to develop new therapies or medical procedures[34], as already recalled above. Particularly significant for translational research are the elements regarding *Potential individual benefits and risks of research* (Guideline 4), which 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

[29] NATIONAL INSTITUTE OF HEALTH, *Translational Science Spectrum*, 2015, cit.

[30] THE EUROPEAN SCIENCE FOUNDATION (ESF), *Implementation of Medical Research in Clinical Practice*, 2011, cit.

[31] EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE), *Statement on Gene Editing*, 2016, available at https://ec.europa.eu/research/ege/pdf/gene_editing_ege_statement.pdf, last visited 08/04/2019, pp. 2.

[32] EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE), *Statement on Gene Editing*, cit., p. 1.

[33] EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES (EGE), *Statement on Gene Editing*, cit., p. 2.

[34] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., *Preface*. All the guidelines are relevant for translational research.

in a two-step process[35]: as first step, the potential individual benefits and risks of research must be evaluated; as a second one, the aggregate risks and potential individual benefits of the entire study must be assessed[36]. 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. In addition, also Guideline 5 (*Choice of control in clinical trials*) is particularly important in the context of translational research. As a matter of fact, 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[37]. CIOMS Guideline 6 (*Caring for participants' health needs*) 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 needs, during and after the research[38].

3. Informed consent in translational research

In the context of translational research, informed consent plays a central and specific role. As in biomedical research in general, "informed consent should be understood as a process, and participants

[35] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 4 (*Potential individual benefits and risks of research*).

[36] 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 (see CIOMS, cit., Guideline 4, *Potential individual benefits and risks of research*).

[37] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 5, *Choice of control in clinical trials*).

[38] See CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 6, *Caring for participants' health needs*).

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have a right to withdraw at any point in the study without retribution"[39]. Starting from the ethical issues related to translational research, namely uncertainty, risk, safety of research participants, three specific points should be underlined, in particular: risk communication, which is of paramount importance in the case of translational research; the patient-physician relationship; informed consent obtained from healthy volunteers, as it is the case of experimental vaccines. We will also offer a brief reference to informed consent during disease outbreaks, a situation which may require the use of unproven treatments.

Subjects 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. As in general, in non-therapeutic studies individuals must give voluntary and written consent[40]. 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 far more true in the case of 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.

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

[39] CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Guideline 9, *Individuals capable of giving informed consent*. As know the principle of informed consent in biomedical research has its origins on in the international institutional level in the Declaration of Helsinki, 1964, last revision 2013.

[40] WHO, *Guidelines for good clinical practices (GCP) for trials on pharmaceutical products* (1995), available at https://apps.who.int/medicinedocs/pdf/whozip13e/whozip13e.pdf, last visited April 26th, 2019. The document contains useful reference to informed consent in clinical trials: 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.

study and research phase provided before, during and after the study. If not addressed, communication barriers between the participants and the researchers may influence comprehension of potential benefits and risks related to clinical studies, leading to misconceptions with respect to an overestimation of envisaged benefits deriving from inclusion in a clinical trial (the so-called "therapeutic misconception"[41]) or in general for the expectation of receiving health services in the context of severely resource constraints public health systems[42].

Another specific aspect of translational research concerns the fact that it presupposes 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. In this perspective, informed consent is a double way process: "Informed consent is a two-way communicative process that begins when initial contact is made with a potential participant and ends when consent is provided and documented, but can be revisited later during the conduct of the study. Each individual must be given as much time as needed to reach a decision, including time for consultation with family members or others. Adequate time and resources must be provided for informed-consent procedures"[43]. 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. Communication of risks is very important as CIOMS recommends in general[44]. 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.

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[41] See C. PETRINI, *From bench to bedside and to health policies (and back): ethics in translational research*, cit., p. 66, par. on "Therapeutic misconception").

[42] Among i-CONSENT findings, D1.7, *Socio-cultural, psychological and behavioral perspectives toward informed consent process*, available at https://i-consentproject.eu/wp-content/uploads/2019/01/D1.7-Sociocultural-psychological-and-behavioural-perspectives-towards-informed-consent-process.pdf, last visited 26/04/2019, explicitly deals with this aspect from a socio-cultural point of view, in particular in section n. 4.4, "Therapeutic misconceptions and unrealistic optimism in clinical trials", pp. 49-54.

[43] CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., *Commentary on Guideline 9, Individuals capable of giving informed consent*.

[44] "Researchers must be completely objective in discussing the details of the experimental intervention, the pain or discomfort it may entail, and known risks and possible hazards. In some types of prevention research, potential participants must receive counselling about risks of acquiring a disease and steps they can take to reduce those risks. This is especially true of preventive research on communicable diseases, such as HIV/AIDS" (CIOMS, *International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, cit., Commentary on Guideline 9, *Individuals capable of giving informed consent*).

General orientations for the obtaining of informed consent are valid for patients and for healthy volunteers[45] as well. Clinical trials for experimental vaccines can be considered part of translational research, as an example of clinical research involving humans; in this specific case, researchers deal with healthy volunteers. 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 ensures quality, efficacy and safety; within the European Union human vaccines are regulated by European Medicines Agency (EMA). 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[46]. Accordingly, risk communication must be deepened and carefully assessed. In the 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.

Translational research, accelerating the process from the lab side to treatment, includes also the reference to the use of unproven interventions, such as the case of the using of vaccine in disease outbreaks. 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"[47]. 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 ob-

[45] On the inclusion of healthy volunteers in clinical trials, the International Bioethics Committee in 2008 recalled that "in dealing with healthy volunteers, the significant fact is that those persons have not, in the first place, requested care/involvement in a medical procedure. They agree to be part of research, either for altruistic reasons or to seek compensation in some other way. The risks involved in the research should be minimized. A description of the research procedures, known risks, uncertainties and participant responsibilities should be provided in order to achieve informed consent. Undue incentives should not be offered to participants and adequate insurance covering adverse events and outcomes should be provided. Participation should be described in precise terms in writing and written informed consent should be mandatory" (UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report On Consent*, 2008, available at https://unesdoc.unesco.org/ark:/48223/pf0000178124, last visited April 26th, 2019, n. 42).

[46] A specific reference on the topic of safety of medicinal products is EUROPEAN MEDICINES AGENCY, *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), available at https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf, last visited April 26th, 2019. 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.

[47] WHO, Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO, 2014, available at https://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/, last visited April 26th, 2019.

tained 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". On the same topic, 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[48].

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.

Innovative therapies 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, which is the case of o*ff-label treatment.* It refers to "the use of treatments which differ from those authorised, with a scientific basis of efficacy and tolerability"[49]. 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"[50]. In addition, promoting translational research of advanced therapies has become a priority for scientific communities and national governments[51].

[48] European Group on Ethics in Science and New Technologies (Ege), *The ethical implications of new health technologies and citizen participation. Opinion n. 29*, 2015, cit., p. 27.

[49] European Group on Ethics in Science and New Technologies (Ege), *The ethical implications of new health technologies and citizen participation*, 2015, cit.

[50] European Group on Ethics in Science and New Technologies (Ege), *The ethical implications of new health technologies and citizen participation*, 2015, cit.

[51] F. Belardelli, P. Rizza, F. Moretti, C. Carella, M.C. Galli, G. Migliaccio, *Translational research on advanced therapies*, in *Annali dell'Istituto Superiore di Sanità*, 47 (1), 2011, pp. 72-78. Advanced therapy medicinal products (ATMP) are a new medicinal product category comprising gene therapy and cell-based medicinal products as well as tissue engineered medicinal products.

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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"[52]. 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, always with an approval by the Ethics Committee; in addition, 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[53].

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.

5. The primary duty of safety for research participants in the leap from bench to bedside

First-in man (or "first-in-human") trials are trials with no specific therapeutic objective. They are one of the principal means of translational research and are regulated by soft law orientations. The first-in-human clinical trial is a critical turning point between preclinical studies and first human exposure

[52] The Nuffield Council on Bioethics, *Topic summary: innovative therapies*, 2016.

[53] 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.

and subsequent larger clinical trials in hundreds or (for many vaccines) thousands of subjects[54]. 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 the case of vaccines, 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. Hence, safety for research participants is the most relevant issue at stake when a novel drug or vaccine is for the first time tested on human beings.

The protection of clinical trial subjects is consistent with the principles set out in the Declaration of Helsinki[55]. Concerning issues related to the general duty to protect the subjects who take part in medical research[56] and to implement measures to minimize risk[57], the Declaration states that 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); in particular, 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). In addition, the ICH Guidelines contain references to research involving humans[58]. In particular, as already recalled, Guideline E6 ("Good Clinical Practice") describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and Ethics Committee/Independent Review Boards[59]. Safety for research participants is recommended as a primary duty also from the WHO: by providing a basis both for the scientific and ethical integrity of research involving human subjects, the WHO *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*[60] 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[61].

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[54] K.B. GOETZ, M. PFLEIDERER, C.K. SCHNEIDER, *First-in-human clinical trial with vaccines – what regulators want*, in *Nature Biotechnology*, 28 (9), 2010, pp. 910-916: "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 comparison to therapeutic proteins or other medicinal products, however, the prophylactic character and mechanism of action of vaccines warrant particular attention" (p. 910).

[55] WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki* (1964, current version 2013), cit.

[56] See WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki*, cit., in particular articles 4, 6 and 7.

[57] See WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki*, cit., in particular articles 16-18.

[58] In particular, among the INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) *Efficacy Guidelines*, which concern the design, conduct, safety and reporting of clinical trials, we remind here: 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).

[59] In ICH guidance, there are references to informed consent, intended as 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 (ICH, *Guideline on Good Clinical Practice* (E6), 1996, n. 1.28).

[60] WHO, *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*, 1995, cit.

[61] The Guidelines also recall that the investigator must take appropriate measures to ensure the safety of clinical trial subjects, underlying in particular that in research on man, the interest of science and society should

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A specific reference on this topic of FIM is the EMA *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*[62]. 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. This Guideline has the aim to increase the regulations on safety of the first testing of a drugs or a vaccine. 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: first in man studies have mainly the scope of establishing this criteria, in order to be then followed from by the subsequent phases of the clinical trial. The EMA 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; it also 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[63]. 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 and risk mitigation activities should be proportionate to the degree of

never take precedence over considerations related to the wellbeing of the subject (WHO, *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*, 1995, cit., Annex 1).

[62] EUROPEAN MEDICINES AGENCY (EMA), *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*, 2007 (first revision July 2017), cit.

[63] The contents of EUROPEAN MEDICINES AGENCY (EMA), *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Clinical Trials with Investigational Medicinal Products*, 2007 (first revision July 2017) are recalled and discussed in K.B. GOETZ, M. PFLEIDERER, C.K. SCHNEIDER, *First-in-human clinical trial with vaccines – what regulators want*, 2016, cit., pp. 910-916.

uncertainty and the potential risks identified. Following the EMA Guideline, it should be added that 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). A balanced and reasonable approach for first-in-human studies of a novel drug or vaccine candidate is crucial to ensure safety of trial participants. The principles of the EMA guideline need to be applied in a reasonable and scientific way based on how prophylactic and therapeutic vaccines against infectious diseases function[64].

The Council of Europe[65], although it does not refers explicitly to translational research or first-in-human trials, offers references regarding ethical issues related to research involving humans: 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.

[64] K.B. Goetz, M. Pfleiderer, C.K. Schneider, *First-in-human clinical trial with vaccines – what regulators want, in Nature Biotechnology*, 2016, cit., p. 916.

[65] The Council of Europe-Steering Committee on Bioethics, *Guide for Research Ethics Committee Members* (2010), par. 6.C.2, p. 29.

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