Horizon 2020 SwafS-17-2016

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

Grant Agreement No:	741856
Project acronym:	I-Consent
Project title:	Improving the guidelines of informed consent, including vulnerable populations, under a gender perspective

Task 2.6
New strategies for increasing participation of patients from diverse cultural and religious backgrounds in clinical trials

Nature:[1]	R
Dissemination level :[2]	Public
Due date of delivery :	30 April 2019
Actual date of delivery :	26 April 2019
Document version :	Final version

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Revision:	Comments on the first draft have been received by : Prof. Stefano Semplici, former Chair of UNESCO International Bioethics Committee, Full Professor of Moral Philosophy at Università degli Studi di Roma – Tor Vergata Prof. Johannes JM van Delden, Chair of UNESCO International Bioethics Committee, Full Professor of Medical Ethics at the Julius Center for Health Sciences of the Medical School of Utrecht University Prof. Barbara Prainsack, Member of the European Group on Ethics (EGE), Professor at Vienna University, Department for Political Science

[1] **R** = Report, **DEM** = Demonstrator, prototype, **DEC** = Websites, press & media actions, videos, **OTHER** = Software, technical diagram, etc

[2] **PU** = Public, **CO** = Confidential, restricted under conditions set out in Model Grant Agreement

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 741856.

Document Information

Contract Number	741856	**Acronym**	I-Consent
Full title	Improving the guidelines of Informed Consent, including vulnerable populations, under a gender perspective		

Deliverable	**Number**	D2.4	**Name**	Executive summary report on ICT-based strategies for increased patient involvement and improved informed consent process
Task	**Number**	2.6	**Name**	New strategies for increasing participation of patients from diverse cultural and religious backgrounds in clinical trials
Work package	**Number**	WP2	**Name**	Innovation in informed consent
Date of delivery	**Contractual**	30/04/2019	**Actual**	26/04/2019
Nature	☑ R (Report) ☐ DEM (Demonstrator/Prototype) ☐ DEC (Websites, press & media actions, videos) ☐ OTHER (software, technical diagram)			
Dissemination Level	PU x CO			
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Revision History

Revision	Action	Date	List of changes	Author Responsible
V1.1	Peer review	29/03/2019	None: first draft	Laura Palazzani
Final version	Submission to D2.4 leader (OPBG) and Project Coordinator	30/04/2019	Edited version after peer review	Laura Palazzani

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Research protocol

GENERAL INFORMATION

TASK TITLE:	New strategies for increasing participation of patients from diverse cultural and religious backgrounds in clinical trials
TASK DESCRIPTION:	Based on the findings of WP1, the task aims at identifying innovative strategies for an active engagement and participation of diverse ethnic and religious groups in clinical trials, taking into account also the characteristics and opportunities offered by new social media and ICT tools.
TYPE OF STUDY:	Analysis of literature, institutional documents, with definition of new strategies
LEADING PARTNER:	LUMSA
CONTRIBUTING PARTNER(S):	None

Background/Purpose

Informed consent is not only a written form or a bureaucratic procedure, but, above all, an essential communication process between the participant and the researcher in clinical research. In many cases, obtaining informed consent may be difficult with people from diverse cultural and religious backgrounds. These individuals/groups are likely to become particularly vulnerable in cases where there are communication barriers between the participant and the researcher, which may hinder understanding of potential benefits and risks related to clinical studies, that can turn out to be a huge challenge in terms of appropriateness, completeness and clarity of information.

In addition to the translation of informed consent in the language of people taking part in the research, an intercultural communication between the researcher and the prospective participant may be required, with a review of the contents through the advice of cultural mediators and cultural insiders, in order to tailor the informed consent to the prospective participant's cultural background. Informed consent as a process should respect the values and the needs of the people to whom the research study is addressed.

Furthermore, the use of digital tools may allow a better understanding of the research process, overcoming communication barriers and misconceptions. Digital technologies can also help to improve the readability and the comprehension of relevant information related to clinical studies and ensure an appropriate awareness in potential participants from different cultural and religious backgrounds with regard to their choice to enrol in clinical research and, once this decision has been made, to stay in a clinical study, fully understanding all possible benefits and risks participation may entail, as well as the uncertainty of research outcomes.

The purpose of this task is to envisage innovative strategies to improve the informed consent process with regard to participants from different cultural and religious backgrounds in clinical trials, based also on the characteristics and opportunities offered by new social media and ICT tools.

Objectives

WP1 findings show that cultural differences between researchers and potential participants in clinical trials can result in communication barriers, which are likely to hinder awareness and pose challenges to the informed consent process. In order to improve this process with regard to participants from diverse cultural and religious backgrounds in clinical research, it is important to adopt procedures that incorporate an intercultural sensitive approach, which includes a deep understanding and respect for people's cultural and religious backgrounds, to guarantee fairness and equity in research participation.
An adequate training of researchers regarding knowledge of main cultural patterns involved in interaction with potential participants is another key aspect for a culturally-sensitive informed consent process. In a context of cultural diversity, it may become significantly challenging to ensure an effective benefit-risk communication between researchers and participants, in order to prevent misconceptions with respect to an overestimation of envisaged benefits deriving from inclusion in a clinical trial.
The objective of this task is to consider cultural challenges in the informed consent process, in order to increase the participation of people of different cultures and religious beliefs, insofar as these elements can influence prospective participants' views about clinical research: overcoming communication barriers means conducting efforts to provide the necessary research information, by considering diverse cultural values and religious beliefs, and to take into account people from different cultural and religious backgrounds during the development of information materials and tools; therefore, envisaging an active engagement of these subjects in the definition of communication strategies (i.e. not only as end users, but also as actors to design the information process).
Innovative strategies, as a result of this literature review and analysis, will focus on explaining how consent can effectively be handled as a process, by checking what are the values and needs involved in a clinical study and take these into account to improve the consent process.
Furthermore, this analysis will verify whether reliance on technological developments in information, which offer new opportunities for the implementation of informed consent, as well as the selection of digital tools according to cultural patterns, may help to modernize and improve the informed consent process, overcoming possible communication barriers between researchers and participants in clinical trials.

Based on the findings of WP1 and on the review of scientific literature, institutional documents, opinions of International, European, national bioethics committees, this task aims at proposing innovative strategies for improving the informed consent process with regard to participants from different cultural and religious backgrounds in clinical trials.

Results will be discussed with international experts in the field and cultural mediators coming from hospitals and health structures:

- *Ospedale Pediatrico Bambino* Gesù – OPBG, Roma, partner of the I-Consent project and prominent institution at international level in the field of paediatric clinical practice and clinical trials.

- *SAMIFO – Salute Migranti Forzati*, Roma, institution that specifically promotes healthcare for forced migrants, in cooperation with the local sanitary service (ASL Roma 1).

Specific objectives

1. To analyse the findings of WP1 related to the task's general objective.
2. To analyse literature concerning communication strategies, participants' satisfaction and understanding of the informed consent process, with reference to clinical research involving people from different cultural and religious backgrounds, including the case of multicentric studies, which are carried out in developing countries.
3. To analyse institutional documents issued by International and European organizations and opinions/recommendations of International, European and national bioethics committees tackling ethics issues related to the involvement of participants from diverse cultural and religious backgrounds in clinical research.
4. To analyse innovative strategies for informed consent in clinical research, with a specific focus on the use of ICT tools, and check whether and how reliance on digital tools can help overcome cultural barriers between researchers and participants in the informed consent process.
5. To assess if the gender perspective is taken into account in the informed consent process involving people coming from different cultural and religious backgrounds, within the sources mentioned in points 2 and 3.
6. To draft a first summary of the results, including recommendations concerning informed consent and cultural aspects.
7. To discuss results and recommendations during the workshop with international experts of the UNESCO International Bioethics Committee (IBC) and during the workshops with cultural mediators.
8. To draft a final version of the summary for the implementation of D2.4.

Methodology

Definition of the research

Analysis of WP1 findings; narrative review and analysis of literature, opinions/recommendations of bioethics committees, institutional documents concerning an intercultural communication in the informed consent process with regard to participants coming from different cultural backgrounds in clinical research.

Analysis process

The search, selection and analysis process will be carried out as follows:

1- A team of researchers will independently carry out the research following the inclusion and exclusion criteria.
2- A different team of experts will screen and assess if the studies found are relevant and meet the inclusion criteria.
3- The team of researchers will include the main findings and results in a final draft, containing recommendations.

Discussion of results

Experts from academia and professionals working in the field, having considerable expertise (also at the institutional level) in the subject of this task, will be invited to a workshop with i-CONSENT researchers involved in the elaboration of 2.6 draft document, in order to acquire insights and opinions useful for the development of the summary.

In particular, international experts from UNESCO International Bioethics Committee (IBC) will read the draft before the workshop and prepare a brief written contribution including comments on this document.
The workshop will be organized with the following purpose: 1) to discuss comments elaborated by IBC experts on i-CONSENT findings regarding informed consent for participants from diverse cultural and religious backgrounds in clinical trials; 2) to identify any gap in i-CONSENT work and suggest actions to improve strategies aimed at improving awareness in participants from diverse cultural backgrounds in clinical trials.

Executive Summary

Aims and scope

Cultural differences between researchers and potential participants in clinical trials could result in communication barriers, which are likely to hinder awareness and pose challenges to the informed consent process. In order to improve this process with regard to participants from diverse cultural and religious backgrounds in clinical research, it is important to adopt procedures that incorporate an interculturally-sensitive approach to communication.

The purpose of this literature and ethical guidelines' review is to consider cultural challenges in the informed consent process, in order to increase participation of people of different cultures and religious beliefs. By "increasing participation", we mean focusing on avoiding an unfair exclusion of subjects from diverse cultural backgrounds (and religious, insofar as religion influences culture generating communication barriers, that can cause someone not to participate in a clinical study due to their religious beliefs) from clinical research.

Cultural diversity includes several cultural elements that can affect health, such as nutrition, gender differences, the family structure, the concepts of autonomy and solidarity.

The objective is to make sure that cultural/language/ barriers in the communication process do not exclude these populations from accessing potential benefits, in those cases where they are envisaged in the study design. Overcoming culturally-driven communication challenges may ultimately lead to an improved access to research participation.
Therefore, an intercultural approach to communication and a participatory approach to the informed consent process (e.g. taking into account the perspectives of different cultural groups in the development of information materials, etc.) can empower culturally-diverse subjects to make autonomous decisions with regard to their participation/non-participation in clinical research.

The analysis of findings focuses also on verifying whether reliance on technological developments in information, which offer new opportunities for the implementation of informed consent, as well as the selection of digital tools according to cultural patterns, may help to modernize and improve the informed consent process, overcoming possible communication barriers between researchers and participants in clinical trials.

Methodology

The report adopts a narrative approach.

This summary of findings reviews current literature on communication strategies, participants' satisfaction and understanding of the informed consent process, with reference to clinical research involving people from different cultural and religious backgrounds. An analysis has also been conducted on institutional documents issued by International and European organizations and opinions/recommendations of International, European and national bioethics committees tackling ethics issues related to the involvement of participants from diverse cultural and religious backgrounds in clinical research, also with a gender perspective.

Based on the findings of WP1 and on the review of scientific literature and institutional documents, this task aims at proposing innovative strategies for improving the informed consent process with regard to participants from different cultural and religious backgrounds in clinical trials.

For further information, see Research Protocol.

Main findings

First of all, the report underlines communication barriers to recruitment of research participants in multicultural and multicenter clinical trials. Among main barriers in cross-cultural communication, there could be language barriers, lack of awareness about trials, lack of trust in research and low health literacy. Communication barriers between the participants and the researchers may influence comprehension.

Furthermore, with specific reference to people with low levels of education or poor socio-economic conditions, researchers should place special emphasis on identifying the socio-economic vulnerabilities that may interfere with the self-determination of individuals and lead to a diminished awareness of potential risks and benefits.

An intercultural communication in the informed consent process could facilitate potential participants' comprehension. Strategies (such as the involvement of family, cultural insiders, cultural mediators during the consent process) should be adopted to overcome language and cultural barriers and contribute to a better inclusion of people from diverse religious and cultural backgrounds.

The report equally highlights barriers related to the interaction between gender and multicultural issues in cross-cultural communication. It is necessary to adopt consent procedures tailored to local cultural and social patterns. Some culturally-sensitive strategies for the inclusion of pregnant women in clinical research are stressed.

There is a significant focus on new methods to overcome communication barriers and improve the informed consent process with regard to participants from different cultural and religious backgrounds in clinical trials. For this purpose, innovative strategies, such as the use of digital instruments, videos, animations, interactive tools, electronic consent procedures, are analysed and discussed.

The opportunities offered by new social media and ICT tools should be taken into account. Ethical challenges related to the use of ICT and social media in clinical research are underlined and some issues, such as the "digital divide" with regard to access to technologies and risks related to data processing and protection of privacy.

1. First section – The informed consent process involving participants from diverse cultural and religious backgrounds: barriers and challenges to global clinical research

1.1 Communication barriers to recruitment of research participants in international multicenter and multicultural clinical trials

Informed consent is not only a written form or a bureaucratic procedure, but, above all, an essential communication process between the participant and the researcher in clinical research. In many cases, obtaining informed consent may be difficult with people from diverse cultural and religious backgrounds, as it is in the case of international multicenter studies where researchers and the potential participants belong to different cultural contexts (see Ten Have 2013, p. 154).

In order to overcome communication barriers and avoid misconceptions and misunderstandings, interaction in a multicultural setting cannot overlook cultural diversity, as it contributes to shaping subjective identities, thus, it impacts on the way people process and understand information.

The UNESCO *Universal Declaration on Cultural Diversity* sets out that "culture takes diverse forms across time and space. This diversity is embodied in the uniqueness and plurality of the identities of the groups and societies making up humankind (…)" (Article 1, UNESCO 2001). It equally stresses that "the defence of cultural diversity is an ethical imperative, inseparable from respect for the dignity of the human person" (Article 4, UNESCO 2001). Culture refers to "the set of spiritual and material, intellectual and affective traits that characterize a society or a social group" (UNESCO 2001); moreover it "encompasses in addition to art and literature, lifestyles, ways of living together, value systems, traditions and beliefs" (UNESCO 2001).

It is important to keep in mind that cultural diversity and religious diversity do not overlap, as in the same cultural group one can find different religious beliefs, and the same religious group can embrace diverse cultural patterns.

As highlighted by the Italian National Bioethics Committee, cultural backgrounds influence individual and collective behaviours: in the researcher-participant relationship, the researcher acts according to his/her heritage of knowledge grounded in medical and professional education/experience gained in particular cultural and social contexts, whereas culturally heterogenous participants may carry with them a broad spectrum of cultural values and religious beliefs, which influence their lifesyles, health habits and views of medical interventions and therapies, different understandings of modesty in public areas, and more generally, different philosophical interpretations of medical duties, goals and practices (i.e. diverse concepts of health, illness, disease, corporeity) (NBC 2017).

i-CONSENT WP1 findings (in particular D1.4, *Ethical issues concerning informed consent in translational/clinical research and vaccination*, and D1.7, *Socio-cultural, psychological and behavioural perspectives toward informed consent process*) show that cultural differences between researchers and potential participants in clinical trials could result in communication barriers, which are likely to hinder awareness and pose challenges to the informed consent process (see also Schroeder, 2018). In 2015 WHO underlined that "a challenge in global health ethics concerns international research, especially where investigators from wealthy countries conduct research in impoverished settings where participants are especially vulnerable or where language and cultural barriers make informed consent difficult" (WHO 2015).

In cross-cultural communication – as in the case of certain international multicenter clinical trials –special care is recommended in collecting informed consent, in order to avoid the risk of possible poor communication due to language differences (see UNESCO 2008; Council of Europe 2012, CIOMS 2009, CIOMS 2016). The difference of values and beliefs (even if not limited to cases of multicultural settings) could generate difficulties in communication itself (see EGE, *Ethical aspects of clinical research in developing countries. Opinion n. 17*, 2003): for example, certain cultural practices and expectations may impact negatively on communication to prospective participants in clinical trials, e.g., in some settings the belief that for a medicine to be effective it has to be bitter or it must hurt (see CIOMS 2005, *Drug development research in Resource-Limited Countries*). Sound comprehension of information can moreover become complex when those who intervene do not use the same references in approaching health problems (for example the scientific approach of a research team is different from a mystic, supernatural approach to health which could be found in some communities) (see UNESCO IBC, 2008, n. 106).

Regarding the specific case of vaccination, WHO 2017 (*Workshop on Expanded Access to experimental Ebola vaccines during outbreaks*) reminds that as far as communication is concerned, "it is critical to ensure that language and communication are clear. People very often associate vaccination with mass vaccination campaigns, and have preconceived expectations about what this means, their potential role and who is vaccinated. Ring vaccination will happen in the context of an outbreak, thus it is critical to get key partners involved quickly to ensure that correct and coordinated messages are given to stakeholders and communities. Communicating who needs to be vaccinated and why must be made absolutely clear. Concerns must be addressed at community level for people who are getting vaccinated, and for people who are not"; the same document suggest the use of a language sensitive to local customs.

Main barriers in cross-cultural communication can be identified with:

a) language barriers (Boddy 2014, George 2014, Quay 2017, Amorrortu 2018, Condon et al. 2019, Schroeder 2018, Palazzani 2019); in some communities there could not even be the word to express some scientific concepts related to research, e.g. for the term 'randomization' (Okello 2013); a study from UK about the inclusion of non-English-speaking patients in research reported language barriers and the unavailability of translators for different reasons (Bernier 2018);

b) lack of awareness about trials and in particular low understanding of the concept of research, which may be confused with the direct health services provision; in general, difficulties in understanding research process (Boddy 2014, George 2014, Quay 2017, Amorrortu 2018, Palazzani 2019, pp. 16 e 17);

c) lack of trust in researchers and low health literacy regarding immunization; concern about adverse events and fears about exploitation (especially in the case of healthy volunteers, as it is in the case of experimental vaccines) (Boddy 2014, Quay 2017, Amorrortu 2018, Browne et al. 2018, Gehlert 2018, Boden Abala 2015).

In this summary of results, we will focus mainly on language barriers (see above, *a)*). If not addressed, communication barriers between the participants and the researchers may influence comprehension of potential benefits and risks related to clinical studies (see Boddy 2014, Bernal 2014, Quay 2017, Amorrortu 2018, Bernier 2018), leading to misconceptions with respect to an overestimation of envisaged benefits deriving from inclusion in a clinical trial (the so-called "therapeutic misconception") (see Marshall 2007, Palazzani 2019) or in general for the expectation of receiving health services in the context of severely resource constraints public health systems (see Amorrortu 2018). On this aspect, the US National Bioethics Advisory Commission recommends that researchers working in developing countries should indicate in their research protocols how they would minimize the likelihood that potential participants will believe mistakenly that the purpose of

the research is solely to administer treatment rather than to contribute to scientific knowledge (US National Bioethics Advisory Commission 2001, Recommendation 3.10).

1.2 The impact of socio-economic factors on participation in clinical trials

International ethical guidelines (WMA 2013; CIOMS 2016; the Nuffield Council on Bioethics 2002, 2005; the US National Bioethics Advisory Commission, 2001) recommend avoiding the so-called double standard in ethics, by mandating that the same standard be applied to research participants in international multicultural multicenter studies. Accordingly, studies that could not be conducted in a high-resource country should not be implemented in a low-resource setting. In particular, a research can be conducted in a low-resource setting, only if is proved that the research is needed to provide new knowledge about the best means of addressing a health condition of that community or region (CIOMS 2016, Commentary on guideline 2, *Research conducted in low-resource settings*). P. Marshall underlines that "the problem of balancing universal and local standards for ethical conduct in biomedical or behavioural research is challenging when investigators confront the very practical constraints of implementing a study in areas where traditional customs may be in conflict with international guidelines, in impoverished nations that bear a disproportionate burden of disease morbidity and mortality, and in areas that lack adequate health resources" (MARSHALL 2007).

Researchers should place special emphasis on identifying and addressing:

a) social and economic vulnerabilities which may interfere with the self-determination of individuals and lead to a diminished awareness of risks: some contextual aspects that fuel social vulnerability in research concern poverty and low educational levels, difficulty in accessing healthcare; see also par. 2.1.
b) undue influence: respect for free and informed consent acknowledges that potential research participants must not be coerced or unduly influenced by use of inducements or threats. As recalled by the CoE Steering Committee on Bioethics, "it is extremely difficult to achieve a complete lack of influence, but influence that would lead individuals to accept a higher level of risk than would otherwise be acceptable to them, would be considered undue. This kind of influence may be financial in nature, but could also include, for instance, attempts to influence family members (as in the case of vulnerable women accustomed to social conditioning to submit to authority), or veiled threats (for example by researchers, medical staff or healthcare providers) to deny access to services to which individuals would otherwise be entitled, or expectation of any other retaliatory response from senior members of a group with a hierarchical structure in case of refusal to participate in a trial. Therefore, special care is needed in situations where participation in a research project may be the only way to access health care" (CoE Steering Committee on Bioethics 2012, 10).

Palazzani underlines that "the application of general ethical standards of clinical trials to the different cultural context, in particular to developing countries, needs an activity of interpretation and specification. In an ethical framework that recognises the priority of the human dignity and justice emerges the necessity of additional standards of safeguard to avoid exploitation or abuse of particularly vulnerable population because of poverty, lack of education and understanding of scientific issues, lack of technical skills, scarce resources, disease, inability to have access to the most basic and essential health products and services" (Palazzani 2019). Some strategies on intercultural communication and an interculturally-sensitive informed consent are identified in par. 1.3 and 1.4.

1.3 Reconciling autonomy with community: an intercultural approach to communication

International guidelines for scientific research involving humans recommend individual, free and informed consent as a general ethical standard (WMA 2013, art. 25; UNESCO 2005, art. 6; CIOMS 2016). The same ethical guidelines highlight that consent presents always a social and cultural context that must be taken into account and respected (see UNESCO 2005; UNESCO 2008; CIOMS 2016; MARSHALL 2007). This is particularly important in the case of some international scientific research, when subjects with different cultural backgrounds are involved in clinical trials, at least as potential participants.

In 2008 the International Bioethics Committee remarked that "there is a difficulty in aligning the autonomy of individuals which is a general ethical standard with certain cultural settings where communal autonomy might be thought to prevail. The expression of an individual wish that goes against these decisions can be difficult or impossible either out of fear of negative consequences for the individual (social disapproval, exclusion…) or out of respect for the leader" (UNESCO 2008, III.3.3, n. 114). As a matter of fact, there are cultures in which the community perspective can prevail on individual informed consent, (e.g. see EKMEKCI and ANDA 2018, ANDOH 2016); or there are communities, such as some south Asian ones, where there are decisional hierarchies within families (see QUAY 2017); moreover, in many settings community leaders or family members play an important role in the decision-making process for participation in research (see MARSHALL 2007, p. 6 and pp. 27-31).

To respond to this challenge, "it is necessary that the issue of consent be envisaged in a more global context of education, making persons autonomous whilst keeping in mind the primacy of the interests of the person concerned in their social setting. It is necessary to ensure the respect for the will of the person concerned, and to promote education towards autonomy and individual responsibility" (UNESCO 2008, III.3.3, n. 120).

This aim can be achieved through an improved intercultural communication in the informed consent process. P. Marshall noted that "when consent is viewed as a process, not a single event, the result is greater flexibility in devising strategies that honour both expressions of individual autonomy and cultural norms regarding the involvement of family members or others who may be important in making decisions about research participation" (MARSHALL 2007, p. 28).

An intercultural communication presupposes embracing intercultural bioethics as the underlying theoretical framework through which to interpret and understand a culturally-sensitive communication, preventing communication barriers, as far as possible, or re-thinking ways to overcome them, by taking into account the intercultural perspective.

Interculturalism values cultural diversity and pluralism, alongside emphasizing integration and social inclusion. As the UNESCO *Declaration on Cultural Diversity* points out "no one can invoke cultural diversity to threaten human rights guaranteed by international law, nor to limit their scope" (UNESCO 2001, Article 4), and it makes clear that "everyone must be able to participate in the cultural life of his choice, and exercise its forms, within the limits imposed by respect for human rights and fundamental freedoms" (UNESCO 2001, Article 5).

In an intercultural approach to communication:

a) it is crucial to overcome stereotypical thinking and a "one for all" communication method, devoting attention to the cultural backgrounds of patients or research participants and to personal specificity among individuals belonging to same culture, contributing to achieve a more respectful, complete and effective informed consent process (see i-CONSENT D1.4, pp. 24-25). Starting from the knowledge of the cultural tradition the researchers

face with, respect is recognized as one of the ethical principles of conduct in research in general but in particular in research in developing countries (see TRUST Project, *Global Code of Conduct for Research in Resource-Poor Settings*, 2018; PALAZZANI 2018, 2019); anything in the nature of the research which the participant may find morally or culturally sensitive should entail some corresponding sensitivity in obtaining consent (see Singapore's Bioethics Advisory Committee (BAC), *Ethics Guidelines for Human Biomedical Research* (2015);

b) the ways of conveying information should be adapted and tailored. EGE remarks that "the way information is given to patients and the procedure of obtaining consent may vary according to the specific situation of the country where a clinical trial takes place, namely regarding the level of literacy, the level of scientific understanding, the organisation of the community, etc. that may influence the consent procedures regarding the involvement of persons, in particular women, in a clinical trial" (EGE, *Ethical aspects of clinical research in developing countries. Opinion n. 17*, 2003, n. 1.29; see also PALAZZANI 2019). Information should be given in a culturally appropriate way (see UN-REDD Programme, 2013; UNESCO 2018, *Policy on engagement with indigenous people*, 2018; in relation to intercultural communication in the specific case of vaccinations, see WHO, *Zika Strategic Response Plan*, 2016). An intercultural approach to communication should be adopted in all cases where there is cultural diversity between the research team and prospective research participants, insofar as this diversity becomes challenging in terms of communication effectiveness and affects the latter's autonomous decision-making throughout the entire informed consent process (before, during, and after the end of a clinical study, in the sense of having the proper information to be able to decide whether to participate in a clinical study, stay in or leave the study at any time without any form of retaliation, an adequate understanding of what is at stake, in terms of benefits and risks, as well as of required behaviours after the end of the study to protect participants' health). This approach to communication involves a global perspective; namely, it can apply both to clinical research conducted within Europe with participants from diverse cultural backgrounds, and clinical research beyond Europe (including but not limited to developing countries).

c) potential participants' comprehension can be enhanced by the researchers through previous consultation with cultural mediators and local representatives regarding the most effective ways of communicating the purpose of the study; investigators might consider conducting focus groups with representatives of those who may be recruited to a study in order to understand issues and concerns associated with preparing the consent form and developing approaches to obtaining consent (Marshall 2007; Chatfield 2018);

d) adopting strategies to safeguard the understanding of the nature and the implications of the research, such as including sufficient time for subjects to consider their participation and discuss it with family and friends; provision of adequate information about what research entails (about research in general and the specific research in particular) from someone without a dependency relationship (such as between physician and patient) (BROWNE et al. 2018);

e) establishing trust is also an important element, alongside with building long-term relationships between the community and the research team (see Marshall 2007, Amorrortu 2018, Van Delden 2017, Chatfield 2018).

In obtaining consent, in some cases, it may be appropriate to obtain before an agreement from the community or from a family member. If a person does not wish to participate, his/her will must always be respected (see EGE, *Ethical aspects of clinical research in developing countries. Opinion n. 17*, 2003, n. 2.7; EMA, *Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation*

applications to the EMA, 2010; TRUST Project, Global Code of Conduct for Research in Resource-Poor Settings, 2018, art. 9, *Community assent*).
A 'relational' view of autonomy, which includes in the autonomy of the individual also the reference to the dialogue with the researcher/physician as well as with wife/husband/relatives (see Italian NBC 2017, *Migration and Health*, i-CONSENT D1.4 *Ethical issues concerning informed consent in translational/clinical research and vaccination*, Palazzani 2019) can provide solutions to ethical and practical problems in clinical practice and research (see Dove and Prainsack et al., 2016; i-CONSENT D1.4).

1.4 Elements for an interculturally-sensitive informed consent

Given the social and cultural context of informed consent recalled above, the informed consent process must take into account some aspects, in order to be interculturally-sensitive:

a) through community consultation (see CIOMS 2005; CIOMS 2009; CIOMS 2016; see also par. 1.3) and other community engagement strategies (see par. 1.5) researchers should verify that informed consent takes into account cultural practices and the health service context. Informed consent procedures should be tailored to local requirements to achieve genuine understanding (see TRUST 2018, in particular art. 21: "Lower educational standards, illiteracy or language barriers can never be an excuse for hiding information or providing it incompletely. Information must always be presented honestly and as clearly as possible. Plain language and a non-patronising style in the appropriate local languages should be adopted in communication with research participants who may have difficulties comprehending the research process and requirements");
b) the process of "back-translation" of the informed consent form (after the translation of the consent form in another language, the form is then given to a native speaker who translates the document back to the original language) is a process which ensures the validity of the translated form and provides opportunities for corrections to be made. Particular attention must be given to the appropriate use of local dialects and terminology that effectively communicates the meanings of words to potential research participants (Marshall 2007); with some populations, where the language is generally spoken and not written, there could be offered the possibility to read the document in English but discuss it in the local language (see H3Africa, 2017); pre-testing consent forms with individuals from the study population provides useful direction concerning the need to revise consent forms so that they are meaningful and understandable for study participants (Marshall 2007);
c) in order to overcome communication challenges in the informed consent process, the TRUST project in the report "Research with, not about, communities" stressed the fact that researchers have historically used strategies such as storytelling, performance or theatre, and more recently have looked into using visual tools, such as creating small video clips where a community member explains the research and the consent process in their mother tongue (Chatfield 2018) (see also par. 3.2);

The European Centre for Disease Prevention and Control provided a guide for the cultural adaption of health communication materials, *Translation is not enough* (2016) which introduces an innovative five-step, stakeholder based approach to adapt health communication materials. The guide underlines that translation alone is not enough and country-based users of internationally-produced health communication resources need to be able to read, understand and apply the materials within their own contexts (ECDC 2016), through the implementation of these five steps, which are indeed useful for culturally-tailored informed consent materials:

1. careful selection of materials and process coordinators (including also local content, linguistic and behavioural experts available to implement the required task);
2. early review by content and linguistic experts (this review should be carried out before translation);
3. translation and quality check (a conceptual equivalent – not literal – translation of the reviewed and culturally adapted source documents; the guide suggestions focus on using one translator because multiple translators will often select different words with similar, but not necessarily equivalent, meanings);
4. comprehension testing (a variety of approaches to comprehension testing are mentioned, such as focus groups, interviews and also internet-based panels of respondents);
5. proofreading, design, networking and evaluation (final document should be proofread, designed – including pictures – and delivered, which in the case of informed consent can be done by involving potential participants).

1.5 Community engagement in collaborative research

Community engagement is a recognized ethical requirement in health-related research: "researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results" (CIOMS 2016, guideline 7, Community engagement; see also EGE 2003, n. 2.4, Partnership; CIOMS 2009, guideline 4, Individual informed consent, par. on *Cultural considerations, consultation with community members* et seq.; VAN DELDEN 2017; Chatfield 2018). Community engagement is a form of patient and public involvement (PPI); PPI in research can potentially help researchers make sure that the design of their research is relevant, that is participant friendly and ethically sound (BAGLEY 2016).

"Community engagement is an effort, which can bring many benefits. Amongst these are: for the researchers, a much better understanding of a local situation than helicopter research would allow and access to knowledge and voices, which will enhance research; for the community – assistance with research questions, which can improve local well-being and international engagement and possibly capacity building" (CHATFIELD 2018). Community engagement could be described as a double way process, a mutual aid between the community and the research team and vice versa (see in particular CIOMS 2016; see also, ANGWENYI 2014, CHATFIELD 2018). In particular, community members should be invited to assist in the development of the informed consent process and documents to ensure that they are understandable and appropriate for potential participants. Community engagement practices can also help suggesting how to explain to potential participants concepts that could be difficult to understand e.g. "placebo", "randomization" and can provide information in a culturally-sensitive way (see OKELLO 2013). Potential cultural sensitivities should be explored in advance of biomedical research with local communities, research participants and local researchers to avoid violating customary practices (see TRUST 2018, art. 8, "Respect"), often through the contribution of the local trusted "spokesperson", persons who not only can translate but also help to understand cultural values and perceptions (Chatfield 2018; see also Angwenyi 2014, Halkoaho et al. 2016, Hugson 2016, Condon et al. 2019), one of whom could be a contact person between the community and the research team (Chatfield 2018).

An active community engagement is therefore recommended (see also BROWNE at al. 2018) and strategies and practical advices could be identified as follows:

a) the inclusion of members of the community involved in the clinical trial in the Institutional Review Board, in order to include community views and perspectives in the ethical review of the study (see CIOMS 2009, guideline 4, Individual informed consent, par. on *Community*

review of, and permission for, studies; EMA 2010, n. 3.1, *Local ethics committee and national regulatory authority oversight*, CIOMS 2016). CIOMS 2009, guideline 4, Individual informed consent, par. on *Committee membership*, highlights a particular case: "When uneducated or illiterate persons form the focus of a study they should also be considered for membership or invited to be represented and have their views expressed";

b) to build long-term, mutually beneficial relationships between the community and the research team, to be applied before, during and after research studies with different strategies according to different phases of the research study, for example: engaging in full and frank discussions about the potential benefits and harms that the participants and the community might encounter; ensuring the alignment of the research to local needs; paying the due attention to the impact of the study and the study team upon the participants, their families, the local community and the environment; taking the time to ensure that the implications of the study have been fully understood by participants and the community (see Chatfield 2018);
c) the consultation with community members (see CIOMS 2009, guideline 4, Individual informed consent, par. on *Consultation with community members*; CIOMS 2016; Marshall 2007; Palazzani 2019), in particular on how to work with the community, e.g. providing a forum for discussing and addressing issues arising from participants and community representatives (Angwenyi 2014); an ongoing "dialogue" between the researchers and the community about the proposed study and its potential implications, or a more structured consultation that would document the concerns of a community or a socially identifiable group (see CIOMS 2009, Commentary on Guideline 4, Individual Informed Consent, par. on *Consultation with community members*;);
d) periodical meetings with local health teams to inform them of potential studies, including meeting in the local languages with the key leaders in the community including the village head, the religious leaders; community feedback meetings at the end of the trials also proved useful in informing participants that studies had ended and for sharing study results (IDOKO et al. 2015); collaborative efforts revealed insights about how to convey information about clinical trial participation (WOODSONG et al. 2014);
e) in the engagement of communities for the use of experimental vaccines and interventions, communication and engagement must be initiated early to build trust in stakeholders, implementers and the government, and to limit misinformation; community perceptions, beliefs and consent should be assessed, i.e. pre-identifying trusted influencers and preferred channels/modes -oral, visual, written- of information of target populations; tools for community engagement should be used, i.e. ensuring materials, tools and guidelines available in local and official languages, with visual and oral aids; developing materials and key messages to communicate uncertainty, consent, adverse effects, ring vs. mass vaccination, and how decisions to vaccinate are made (see WHO 2017).
f) in the case of disease outbreaks, community engagement should be reached through social media, in particular as far as preparedness and risk communication is concerned (see WHO 2018, where a useful checklist is provided).

2. Second section – Interaction between gender, culture and education in cross-cultural communication

2.1 Gender and health literacy

There are some specific barriers related to the interaction between gender and multicultural issues in cross-cultural communication, within geographically different research settings. A study conducted by Killawi *et al* in the Arabian Gulf Region (particularly in the high-density multicultural setting of Qatar) describes how prospective research participants perceive their potential participation. As for the participant recruitment procedure, cultural norms in Qatar require that interactions between men and women occur in public space except for purely medical reasons or necessity depending on the task. The mostly Muslim and all-female research assistants felt it would be culturally inappropriate for them to be in a private room with a man. In addition, more women in the Arabic language group declined participation compared to any other language group (they felt compelled to discuss with a family member whether to participate). The study includes some good practices:

a) culturally-competent and language concordant female research assistants were involved in research procedures to avoid breaching cultural sensitivities about gender interactions: relying on male research assistants to recruit female subjects is more likely to clash with cultural sensitivities about gender interactions and thus have a negative impact on the research, compared to female research assistants recruiting male individuals;
b) recruitment took place in "gender specific waiting areas" (Killawi et al. 2014) with female research assistants wearing white research coats to convey their official status and mitigate cultural patterns of gender separation.

In this case, consent procedures were tailored to local cultural and social patterns; this empirical study has led to the conclusion that taking into account cultural influences results in an increased participation rate (Killawi et al. 2014).

Moreover, research ethics guidelines and scientific studies identify a number of recommended practices taking into account women's health literacy:

a) in order to improve the understanding of information: "[…] providing information through health workers (and particularly female health workers when the research will involve women), rather than physicians so that participants feel more able to discuss and ask questions; providing information about a research project in various ways that are appropriate to the community (i.e. in parts of Africa, information has been supplied on audio or video tape, on the radio and through ballad singers); in some communities, particular care will need to be taken to ensure that the methods of providing information and aiding understanding which are adopted will ensure that the information will reach all members of the community. For example, if public meetings are used, it must be borne in mind that young women may feel unable to ask questions during such a meeting" (Nuffield Council on Bioethics, 2002);
b) in order to increase understanding of cervical cancer perceptions and beliefs: Mwaka *et al.* explored community perceptions, beliefs and knowledge, in Northern Uganda, about local names, causes, symptoms, course, treatment, and prognosis of cervical cancer in order to inform targeted interventions to promote early help-seeking. The study suggested "awareness campaigns to promote early help-seeking for cervical cancer

symptoms need to be culturally-sensitive and context-specific; and include messages on symptoms, risk factors, course, treatment and prognoses" (Mwaka *et al.*, 2014);

c) in order to improve awareness of Muslim women health beliefs: a study by Walton et al. suggest that "Muslim women (1) prefer to make autonomous health care decisions without the assistance of a male family member, (2) prefer to have a female health care provider, (3) are willing to access medical and rehabilitation services if provided by a female, but not when provided by a male health care provider, (4) believe in the use of prayer, recitation of Quran, fasting, charity to be beneficial to their physical health, and (5) are comfortable with the use of physical touch in medicine and rehabilitation evaluation and treatment, if the provider is female" (Walton *et al.,* 2014).

Aiming at improving informed consent of women through the use of multimedia tools the following elements should be taken into account:

a) Muhammed Olanrewaju Afolabi *et al.* assessed the effectiveness of a multimedia informed consent tool for adults participating in a clinical trial in the Gambia. A computerized, audio questionnaire was used to assess participants' comprehension of informed consent. This was done immediately after consent had been obtained and at subsequent follow-up visits (days 7, 14, 21 and 28). The acceptability and ease of use of the multimedia tool were tested in focus groups. Poorer comprehension was independently associated with female sex. A multimedia informed consent tool significantly improved comprehension and retention of consent information by research participants with low levels of literacy: research concepts that are known to be difficult to understand were clearly illustrated using video recordings and animations and explained by sound tracks in three local languages (Muhammed Olanrewaju Afolabi *et al.,* 2015).

b) In a study on HIV research in South Africa, Staunton et al. highlight that obtaining consent in low- and middle-income countries can be challenging, and they identify ethical issues in developing an educational video to empower potential participants during consent processes. This tool has been prepared taking into account gender differences and some critical points emerged. Low levels of education, complexity of science and research processes, confusion about basic elements of research, and socio-economic conditions that make access to medical care difficult have led to concerns about the adequacy of the consent process. Evidence showed the importance of early community engagement in educating potential research participants and promoting community acceptance of research. This study reported that a 15-minute educational video entitled 'I have a dream: a world without HIV' was developed to educate and empower potential research participants to make informed choices during consent processes in future HIV cure clinical trials. The decision to include two women as the HIV-positive actors, instead of a male and female actor, turned out to be problematic as it may fuel misconceptions that women are carriers of the disease. In South Africa, women are generally in charge of the care of a child, and thus the caregiver needed to be female; equally, issues such as rape and female contraceptive methods, also required a female actor. This video prototype could be used in research targeted at different populations, and coupled with a variety of different media (Staunton *et al.*, 2018).

2.2 Culturally-sensitive communication on contraception in clinical trials

The use of contraception to avoid pregnancy, as a requirement for participation in clinical research, can become ethically problematic especially when such prescriptive contraceptive methods clash with moral and religious beliefs, resulting in a possible barrier to research enrolment decision-making.

As recalled in Deliverable 1.3, the Italian NBC emphasized the ethical and social relevance of fertile women participation, "provided that an adequate protection of the unborn child can be guaranteed" and provided that the research is relevant for this population group.

A preliminary consultation about the trial is recommended, during which clear and accurate information on the goals of the study is provided, as well as a classification of benefits and risks that the study may involve for the participant, highlighting the risks for the foetus in case of pregnancy. Whenever risks for the foetus are envisaged, the NBC underlined the importance of the woman's clear statement of a conscious and responsible commitment to honour abstinence from sexual activity, in order to avoid pregnancy (NBC 2008, 18). The NBC also highlighted that the informed consent must be guaranteed, giving women a fair amount of time and appropriate environmental conditions to decide, and that their individual consent cannot be replaced by the partner's consent.

The use of contraception is highly controversial and ethically problematic, as in many cases where fertile women are involved research sponsors consider it a mandatory requirement for participation. Despite the existence of a variety of stances on this issue, which reflects an ethical pluralism in our current society, it is possible to identify two main positions that oppose this mandatory requirement: a first one upheld by those who criticize the expectation of the pharmaceutical industry that women should use hormonal contraceptives, as this requirement would restrict women's freedom, intended as self-determination (e.g. the possibility to choose among different options); others also argue that relying on hormonal contraceptives as a mandatory requirement is not morally acceptable, since it would be detrimental to the freedom and responsibility of research participants, but inspired by a different perspective. This position, supported by those who believe in the inseparability of the unitive and procreative dimensions of the conjugal act, claims that the woman's explicit commitment to avoid pregnancy is sufficient, and that she should be able to choose birth control methods, respectful of her lifestyle and values, including abstaining from sexual intercourse (NBC 2008, 12-13).

The Committee on Ethics of the American College of Obstetricians and Gynecologists equally stressed that a woman should be allowed to choose a birth control method, including abstinence, according to her needs and values. In addition, in the Committee's view, "requiring specific contraception in a woman not sexually active violates a commitment to respect her as a person" (Committee on Ethics of the American College of Obstetricians and Gynecologists 2015, 103). This ethical position is in line with the concerns raised by the NBC. As part of the consent process, the woman should be duly informed of all types of risks (including those risks impacting on her decision to enrol or not enrol in research), that could be affecting her and/or her foetus in case of pregnancy (ACOG, 2015).

Moreover, The UK Royal College of Physicians encourages researchers to provide appropriate advice concerning contraception precautions and about the existing option of "emergency contraception" if precautions have been omitted. Nevertheless, this possibility is ethically problematic, since it is likely to deter women not willing to run the risk of jeopardizing a potential pregnancy and harming the foetus from participating in high-risk trials, entailing an under-representation of specific groups of women (Royal College of Physicians, 2007).

2.3 Culturally-sensitive communication for the inclusion of pregnant women in clinical trials

Concerning clinical research involving pregnant women with the prospect of direct benefits for the health of the foetus, there may be cases where participants belong to communities or societies in which cultural beliefs place greater importance on protecting the foetus than the woman's health. In these circumstances, women may feel coerced into enrolling, or not enrolling, in research. Hence, special safeguards are recommended to prevent undue inducement to pregnant women to participate in research with potential benefits to the foetus, but not to the woman herself (CIOMS 2016, Commentary on Guideline 19). Although, cultural issues and the scientific knowledge gap between researchers and participants, directly affecting the latter's capacity to clearly understand the underlying risks related to their specific health condition should be carefully weighed, especially in these sensitive circumstances.

Frew et al. 2014 provides a number of interesting culturally-sensitive strategies for the inclusion of pregnant women in clinical research:

1) community outreach to advise providers about studies: this aspect is key to helping women overcome unease and distrust of the research (the most common reason for women's unwillingness to enrol in studies was identified with a preference for protocols that enabled them to follow-up on study results with their clinician);
2) face-to-face interactions with health providers;
3) health staff education and message training, along with study promotion via clinic media, print material, and interpersonal communication, in order to enhance patient receptivity to recruitment;
4) conducting research within a community space or offering home visits: low-income women may not have reliable access to research study sites, particularly if they rely on a friend or family member for transportation, or use of public transportation;
5) explaining the objective of clinical trials for testing drugs for pregnant women in hospitals and obstetric offices has been successful in identifying and enrolling eligible pregnant women for immunization trials; in general, visits to community groups in their geographic area;
6) giving the possibility to discuss with friends and family members;
7) community engagement strategies, including focus groups among pregnant women to identify important barriers and facilitators to research participation, relying on targeted messages and culturally-sensitive information materials adapted to gender needs and preferences, as well as community-based participatory research methods;
8) accommodation of time constraints of pregnant women by taking advantage of mobile technology and the prevalence of cellular phone usage. For example, the Text4baby (T4B) program, launched in 2011, attempted to improve health behaviour and perceptions among pregnant women by employing a text messaging program. T4B successfully changed attitudes toward pregnant women's health behaviour and thus it is recommended as method to alter perceptions of clinical trial practicality and overall potential benefits to their health. Disseminating messages via cellular phone usage allows investigators to educate eligible participants without taking additional time out of pregnant women's schedules. Education via mobile technology that has promoted significant changes in health behaviours and perceptions may also help providers restrained by clinical duties to reach eligible patients and use a similar program to educate them on available studies. Social networking sites have been employed as an effective method of increasing recruitment rates among pregnant women.

Culturally appropriate messages and research tailored to the need of prospective participants are among the most effective strategies contributing to successful retention of pregnant women in research trials. These findings further evidence the importance of recruitment methodology that is carefully tailored to interests and needs of pregnant women (Frew *et al.* 2014; Martínez Perez e*t al.*, 2018).

2.4 The role of the male partner in the informed consent process

Findings from Deliverable 1.3 show that institutional guidelines are generally keen on not considering women as vulnerable subjects, since this may fuel reticence towards their inclusion in research and hinder the possibility for them of reaping the potential benefits deriving from participation. However, there are a number of circumstances in which they could be vulnerable in research, such as studies with women who live in a cultural context where they are not permitted to consent on their own behalf for participation in research, but require permission from a spouse or male relative. When women in such situations are potential participants in research, researchers need to exercise special care (CIOMS 2016, Commentary on Guideline 15). Particularly, CIOMS guidelines stress the fact that "in many societies women remain socially vulnerable in the conduct of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions, and a cultural tendency to deny or tolerate pain and suffering. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits, as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them" (CIOMS 2016, Commentary on Guideline 18). Caution must be used if vulnerable subjects are enrolled in studies; their proposed participation in a research project must always be justified specifically. The general rule is that potential research participants should be the least vulnerable necessary to achieve the goals of the study and appropriate protection should be ensured in these specific cases, in order to guarantee the dignity and safety of women consenting to participate in research (CoE, Steering Committee on Bioethics 2012, 10).

There is broad consensus in international and European guidelines on the fact that in no case permission by the woman's partner may replace the individual informed consent of the woman herself, since this would result in a violation of the principle of respect for the person. However, if the woman wishes to consult with husband or partner before deciding to enrol in research, that is deemed to be not only ethically permissible, but in some contexts highly desirable (UK Royal College of Physicians, 2007). In addition, different cultures may also have different views concerning privacy and personal data, which can impinge on the acceptability of certain aspects of research protocols, especially with regard to data collection, as well as the data subject's right of access and right to object (The European Group on Ethics in Science and New technologies, EGE, 2003, 13).

The NBC stressed the fact that in some cultural contexts women tend to delegate decisions concerning their health to a partner, a male family member or the family group. In this perspective, the Italian Committee for Bioethics, proposes an interpretation of the concept of autonomy in terms of "relational autonomy", which may be better tailored to an intercultural approach aiming at accommodating the value of the community dimension in certain cultural settings and respect for the person (NBC 2017, 38). In the context of research participation, women living in a social context of patriarchal authority, having a low literacy level, may adopt a passive behaviour with regard to enrolment procedures or not seek interaction with researchers in case of insufficient understanding of the study evolution. Therefore, as stressed by the UK Royal College of Physicians, "research ethics

committees should exercise special care in examining the proposed consent process to ensure adequate time and a proper environment in which a decision to participate can be made" (UK Royal College of Physicians, 2007).

Therefore, involving particularly vulnerable women (for instance those living in poor socio-economic conditions) in clinical research should be carefully assessed, in order to avoid, on one side, any form of discrimination by excluding specific population groups from participation, which can directly (as individuals) or indirectly (as population group) benefit them; and, on the other, to prevent any form of coercion or undue inducement (on undue inducement, see also par., 1.2).

The role of male family members or partners may have a different impact on the woman's decision to participate in clinical research in diverse cultural groups. Looking into a number of geographical and cultural perspectives, the Nuffield Council on Bioethics highlights some considerations about women decision- making:

- in some South Asian regions, "women may not always be able to express personal opinions on even minor matters, let alone the issue of whether they would like to take part in research. The notion that individuals are free to make their own decisions will therefore be less familiar to such women";

- in China, women are usually not expected to obtain the permission of men or elders before deciding to participate in research. However, before consent can be sought, "a visiting research team's proposals will need to be discussed in an open manner through the offices of the village cadre committees";

- in many parts of Africa, women, especially in non-Muslim societies, have developed a more assertive position with regard to healthcare, often aided by mission hospitals, clinics and health focused non-governmental organisations. "As cultures are not fixed, researchers may need to find means of fostering discussion about what is required by cultural norms in a particular context. For example, research in South Africa has shown that even within a culture with strong beliefs about the importance of the community, many women favour the approach of requiring individual consent to research". In addition, in some areas of Uganda with traditional social and cultural values, men (husband/father as the head of the family) are expected to decide on all matters, especially sensitive ones affecting family members. Therefore, family members who do not submit to such decisions may face serious consequences including domestic violence and/or divorce. In this context, "women and children will tend not to participate in a study unless permission has been granted by the head of the household".

- in Latin America, unlike the cultural contexts mentioned above, community consent or other types of group consent are not common practice. Although collective information can be provided to rural communities or ethnic minorities, such as indigenous populations, consent by individual participants is accepted (Nuffield Council on Bioethics, 2002).

In this regard, the US National Bioethics Advisory Commission recommends that "researchers should use the same procedures in the informed consent process for women and men. However, ethics review committees may accept a consent process in which a woman's individual consent to participate in research is supplemented by permission from a man if all of the following conditions are met: a) it would be impossible to conduct the research without obtaining such supplemental permission; and b) failure to conduct this research could deny its potential benefits to women in the host country; and c) measures to respect the woman's autonomy to consent to research are undertaken to the greatest extent possible. In no case may a competent adult woman be enrolled in research solely upon the consent of another person; her individual consent is always required" (US National Bioethics Advisory Commission, 2001).

2.5 Best practices on culturally-tailored health communication programs with a gender perspective

The *Gender guide for health communication programs* issued by the US Center for Communications Programs (2003) points out the importance of including gender concerns in health communication initiatives, aimed at making health messages more effective and foster awareness of the necessity of equity in terms of gender needs. A gender perspective in communication should take into account ways in which gender influences health needs and concerns, different roles and interests of women and men, as well as the reception of health messages. Seeking feedbacks of effective communication strategies is highly recommended, also by conducting evaluations in different cultural communities. It is critical to speak to women and men separately to obtain reliable gender-informed perspectives (see i-CONSENT Deliverable 1.3).

In this context, it is possible to identify a set of culturally-sensitive communication strategies with a gender perspective (i.e. "the ways in which gender influences health needs and concerns, the reception of health messages, and access to and control over health communication interventions", John Hopkins University Center for Communication Programs, 2003):

a) health communication programs should take into account different needs, roles, and interests of women and men; spousal communication and power dynamics between men and women; decision-making processes; social and cultural constraints and opportunities;
b) communication initiatives should assess potential positive and negative program impacts and communication capacity (e.g. access to media for women and men and their media habits: devising which communication channels, radio, tv, print, talks, community meetings, are used by women/men for health information and how this differs according to age and education levels);
c) communication strategies should ensure that services, supplies, and practices of chosen media do not reinforce gender stereotypes;
d) pretesting and re-testing messages, concepts, and intended program formats with women and men separately to determine what works well for women and what works well for men. These materials should be tailored to the different cultural groups they are addressed to.

In the context of a cultural adaptation of information, Brown et al. reported that ethnic-specific information about health risk associated with recipients' health condition increased recruitment of African American women into clinical trials. They provided evidence that "many patients and family members misunderstood trial information and that many felt that a question prompt lists and decision aids would assist in decision-making". In addition, they suggest that the best strategies to reduce enrolment barriers and retain participants are associated with the ability to keep constant contact with participants. Moreover, being respectful and showing a caring attitude are the important factors in this population. The authors equally stress that findings may not be specific to African American population but can apply to other ethnic groups (Brown *et al.*, 2013).

Among the innovative strategies aimed at the inclusion of women from diverse cultural backgrounds in clinical trials, Jones *et al.* illustrate a *Facebook* advertising of a clinical trial with African American women and provide a practical guide to create and publish a Facebook ad for a target population. This approach can be adapted to different study populations in diverse cultural settings. Although online recruitment lacks face-to-face contact, there is evidence that for many, such contact did not deter recruitment. Advertising for enrolment in clinical trials via social networking sites, specifically Facebook, has led to encouraging results in expanding geographic reach while still targeting a population and maintaining confidentiality. A broad representative distribution, including those less accessible via traditional venue sampling due to stigma may be reached online for participation in clinical trials (Jones *et al.,* 2017).

3. Third section – Strategies to overcome communication barriers between researchers and research participants

3.1 Cultural competence training for researchers working with subjects from diverse cultural and religious backgrounds

For an adequate informed consent process, personal interaction between subjects involved in clinical trials and researchers is essential. The informed consent process should be customized to meet the particular needs of individual study participants: it should involve an ongoing, interactive conversation between the research participant and the research staff, during the whole process. For this reason, CTTI Recommendations (February 21, 2019) stressed the need that research staff obtaining consent should be trained to do so. An informed consent training program should aim to improve knowledge and communication skills of researchers.

As described in par. 1.3, communication can be more challenging with participants from diverse cultural and religious backgrounds.

It is therefore recommended that researchers develop cultural competence, namely awareness of cultural influences on patients' health beliefs and behaviours.

Cultural competence of the research team is recognised as very important (Truong, 2014). More specifically, cultural competence training for researchers would guarantee an effective communication and interaction with participants from diverse cultural and religious backgrounds.

Strategies to develop cultural competence of researchers in order to increase the recruitment of participants who are unable communicate fully due to cultural barriers should be promoted. These strategies should include the following aspects:

a) an adequate education of researchers should be promoted: an increase in the intercultural skills of the researchers is recommended, in order for them to be able to interact appropriately with participants from diverse cultures, in the perspective of intercultural communication (see par. 1.3). It could be useful to devote adequate consideration, within university training paths, to studies focusing on the therapeutic relationship in an intercultural perspective (the so-called transcultural medicine);
b) a cultural mediator should be involved in order to overcome language barriers. A cultural mediator is not only a translator; he/she is a professional able to bridge existing gaps between different cultures on the basis of personal skills and experiences. The term 'cultural mediator' is defined in various ways across Europe, but in general, the cultural mediator is always recognised as different from a family member. In clinical research settings, with special reference to the informed consent process, the purpose is creating conditions that are equal for subjects with diverse cultural and religious backgrounds regarding information and decision-making; specific education programs should be prepared for health mediators of different cultures (e.g. see WHO 2013, *Roma health mediation in Romania: case study*);
c) during the consent process a 'cultural insider' should also be involved, i.e. a person who has knowledge of the language and familiarity with the culture of a particular group through their membership in that group (Shariff, 2014). Alongside with community engagement strategies as described in par. 1.5, the 'cultural insider' should facilitate researchers in interactions with

members of the community. Involving cultural insiders helps in gaining a deeper understanding of the sociocultural contexts of the research setting and enables researchers to conduct research with culturally-sensitive methods, as local people will be more inclined to share their feelings and perceptions when they have trust in people recognized as insiders. In this way, the research can be culturally informed at each step of the research process;

d) continuity of the research team: when the researcher who interacts with each participant is the same through the different phases of a clinical trial, this helps build a bond of trust between researchers and prospective participants and maintain consistency in the conveyance of information;

These strategies aim at strengthening an intercultural sensitive approach to communication among researchers and potential participants in clinical trials and may contribute to improve participation of people from diverse cultural backgrounds in research. In this sense, open and understandable communication between researchers and participants during the whole research process could help creating trust in relationship and maintaining consistency in the information, thus, overcoming one of the main barriers in communication.

3.2 Innovative strategies to improve the informed consent process in an intercultural setting

Advances in technology enable novel communication approaches, allowing researchers to adapt the informed consent process to persons of diverse health literacy of all backgrounds (Kaye J. et al., 2015; Meslin E.M. et al, 2013). Apps, tablets, video, interactive computers, robots, personal digital assistants, smartphones, and wearable technology, could help to modernize and improve methods for obtain informed consent. The adoption of digital tools within the IC process could facilitate and develop practices that are more culturally appropriate and that reflect the values, customs, and level of exposure of local communities to research (Jones A.et al. 2013).

At international level, the guidelines include an ethical analysis of the use of digital technologies in healthcare in general. The Report of the International Bioethics Committee of UNESCO (IBC) on Big Data and Health (2017) stressed the importance and problems about informed consent given electronically (informatic consent), specifying that electronic means in clinical research may be efficient and effective as long as there are safeguards implemented to ensure that the participants' autonomy is respected. The CIOMS International Ethical Guidelines for Epidemiological Studies (2009), focus, in the Guideline n° 6, on responsibility of the investigator for ensuring the adequacy of informed consent from each subject. When subjects are enrolled in studies by mail or electronic means (e.g., e-mail, Internet, etc.), difficulties may arise in fulfilling investigators' duties to ascertain that subjects adequately understand relevant facts. Potential subjects enrolled in these ways should therefore be given a means (such as a toll-free phone number or email address) to enable them to pose questions to, and receive answers from, the research team concerning the study.

Tools to provide information are the following:

a) videos: the value of audio-visual interventions as a tool for helping to improve the informed consent process for people considering participating in clinical trials should be take into account. Audio-visual presentations can ensure the clear delivery of information that is complete, consistent and unbiased, to supplement or reduce staff time spent in seeking informed consent. A study of the feasibility of using multimedia technology during the informed consent process for clinical research reported that the use of the video made information more understandable (Synnot A. et al., 2014);

b) animations: a study on 58 focus groups of African Americans, Latinos, Native Hawaiians, and Filipinos in Los Angeles/Hawaii demonstrated that via animation improved the communicating information about health research (Sheba, 2013). After viewing the video, participants appeared to be able to identify gaps in knowledge about research and to express an increased desire to seek information to address these gaps. In addition, the findings also suggest that animations may be augmented when accompanied by a community facilitator or a family member. The advantage of the animations is that are easier to be customized according to the subject's characteristics;
c) interactive tools: in general, interactive tools have a better impact in comprehension of information and long-term memory then non-interactive tools, so a combination of interactivity and animation could be a good solution to design innovative digital-based strategies (Ownby et al. 2015).

Digital innovation and interactivity can indeed play a central role for the success of these strategies. Scientific evidence highlights the positive impact of a strategy blending personal relationship and innovative, video-based and digital tools (Tait and Voepel-Lewis 2015). These techniques could help to overcome language barriers, stressed in the chapter 1 of this report.

A scientific study focused on a self-administered, web-based survey using an experimental between-group design to compare the effects of four informational aids on respondents' understanding of core aspects of research (Kraft 2017). The aim was to verify what methods could improve informed consent in clinical research settings. Multimedia informational aids assessed were the following: animated videos (audio, character-driven); slideshows with voice-over (audio, not character-driven); comics (no audio, character-driven); text (no audio, not character-driven). Findings showed that knowledge scores were significantly higher for the two informational aids with an audio component (animated videos and slideshows with voice-over) than in the two without (comics and text). Consequently, using multimedia informational aids (especially if with audio approach) could help to bridge the knowledge deficit about research.

In the UK, the Guidance of Health Research Authority (HRA), with particular regard to clinical trials, stressed the importance of the use of media or non - text - based approaches (videos, cartoons, animations, info graphic cards, flipcharts, brochures and audio). These methods may be used as patient- friendly introductions to complement, or replace, the traditional paper information sheet.

The Clinical Trials Transformation Initiative (CTTI) developed a Project, with the objective to identify barriers to communication of informed consent elements and develop recommendations for improving the informed consent. Among these:

1) engaging patients and sites to drive adoption of mobile technology in clinical trial; engaging patients and sites in planning clinical trials using mobile technology, including protocol design, technology selection, and pilot testing, in order to enhance satisfaction and engagement, recruitment and trial feasibility. Patients' perspectives can be identified through advisory panels, surveys, focus groups, simulation exercises and other methods (a range of relevant perspectives should be represented, including appropriate and diverse racial and cultural backgrounds);
2) select mobile technologies based on requirements of the study and needs of the intended user population, starting with the aspect that the assessment is intended to measure (engage patients and sites in technology selection; conduct feasibility studies to ensure that study participants find the technologies easy to learn, simple and convenient to use, physically comfortable);
3) when planning a trial using mobile technologies, identify and conduct necessary pilot studies with sites and a representative patient population. Mobile technologies can change the way sites and participants interact during a trial (For example, mobile technology can reduce the need for in-person visits and facilitating participation in the trial).

There is no extensive body of literature focusing specifically on the use of information technology (IT) to improve consent in an intercultural setting. However, improving the consent process for culturally and linguistically diverse population participants has been the focus of several studies, that emphasized the importance of adopting a multi-methodological approach, including the use of culturally and linguistically sensitive multimedia tools, to tailor the information process to the needs of subjects from diverse cultural and religious backgrounds in clinical research. Multimedia resources may have key roles to play in addressing health research literacy by explaining medical research, enabling researchers to assess comprehension through testing, and improving participant comprehension of consent forms and procedures. Furthermore, multimedia tools could be used by researchers, who do not necessarily speak the language of the research participants (Hughson et al., 2016).

Clinical trial participants in sub-Saharan Africa often have limited understanding of the study information provided during the informed consent process. In countries such as the Gambia, where local languages have no standard written form, translating documents into the local language and back translating into the national language is impractical (Afolabi M. O. et al., 2015). In particular, illiterate participants may not understand research concepts and this fact could undermine their ability to give truly and effective informed consent.

A study on effectiveness of the multimedia tool in malaria treatment trial in the Gambia confirmed that use of a multimedia informed consent tool results in significantly better understanding of clinical trial information than the current standard method for obtaining consent (Afolabi M. O. et al., 2015). In the scientific study, the multimedia tool was tailored to the cultural and linguistic diversity of the Gambian population: the visual and verbal information presented through the DVD resulted clear and easy to understand in an area of the Gambia with low levels of literacy.

3.3 Ethical challenges related to the use of ICT and social media in clinical research: e-Consent in an intercultural setting

The expression ‘e-Consent’ refers to the use of any electronic media (such as text, graphics, audio, video, podcasts or websites) to convey information related to the study and to seek informed consent via an electronic device (such as smartphone, tablet or computer). These electronic methods are adopted by researchers either to supplement or substitute the traditional paper-based approach. E-consent may increase understanding of the study, particularly for people with a low educational level or limited literacy.

Most studies have shown that participants’ recall of key facts about a study is better with the use of e-consent with these interactive features than with paper forms (Rosa et al., 2014; Kaye et al., 2015; Simon et al., 2016). However, there are also challenges regarding electronic consent for researchers. First of all, when the consent documents are provided by electronic methods there is the problem to verify the participant’s identity. Additionally, there is the problem of the high initial expense for infrastructure and technology to manage online documents and establish systems to validate electronic consent.

The use of multimedia informational aids in clinical research shows many advantages.

Ensuring participant comprehension continues to be a challenge in e-Consent. A study (Doerr, 2017) focused on assessment of a convenience sample of participant reaction to the e-Consent implementation (within the Parkinson mPower mobile study) using a mixed methods approach.

The starting point was that to fully capitalize on mobile technology we must develop companion self-administered electronic informed consent (e-Consent) processes. Incorporating novel informed consent approaches on a target study population diverse in terms of ethnicity, primary language and health literacy, demonstrating that the use of the electronic consent (e-Consent) not only increases the opportunity to recruit patients culturally isolated, but also has the potential to increase the trust.

A study by Rosa et al. (2015) underlines the advantages of use of technology in clinical trials:

a) communication: technology tools improve communications not just with study staff, but also with patients and communities.
b) recruitment: using apps and social media could increase the number of participants contacted and enrolled.
c) retention: mobile phones/devices, apps, and social media offer the opportunity to connect with participants more often and potentially improve their involvement and retention. Smartphones, apps, and wearable body sensors can allow for large quantities of data to be collected automatically and not require face-to-face interactions with researchers.
d) e-technology-based interventions can reduce resource requirements related to staff training and ongoing supervision, maintain consistent delivery of an intervention.
e) data collection: use of registries can improve targeted recruitment and make standard clinical data available in real-time for study outcome purposes. Digitized forms have been shown to improve data quality.

The use of social media in research consent may improve the quality of the consent process by overcoming awareness issues about trials and in particular low understanding of the concept of research. Furthermore, the use of these methods may improve comprehension issues associated with medical and legal jargon.The influence of ICT and the Internet including social media was an important factor in how healthcare services in Thailand are being offered and practiced. In Thailand, the use of social media for Thai healthcare professionals is emphasized on Facebook and LINE Chat applications. Thailand has achieved an elevated level of access to e-health services and use of ICT (Jantavongso, 2015). The use of social media in research consent allows research participants can open up online dialogue and interaction with professionals and exchange information during the process from anywhere and at any time (O'Connor 2013)

App-based research has the advantage that all or most of the research study can be conducted through the smartphone, from obtaining informed consent to collecting data (Grady, 2017). Conducting health research and obtaining informed consent on smartphones raise several unique challenges and limitations. The most important limitation is that there is no face-to-face confirmation of identity. Another challenge with respect to app-based research is data security and privacy.

a) Despite multimedia tools in clinical research have certainly important advantages, some ethical challenges to the use of digital technologies in informed consent remain, described as follows: first of all, Information Technologies could involve risks related to the processing and protection of privacy and personal data and misuse of these A fundamental challenge lies in ensuring that patient data remain confidential and secure in order to build trust in the use of ICT (EGE Opinion No. 26 2015).
b) the Guideline n° 23 (CIOMS, 2009) provides for that the investigator must ensure that an appropriate informed consent procedure is applied and that data confidentiality is maintained. Subjects' privacy, confidentiality and security are at stake when data are conveyed to others electronically. In this regard, CIOMS, 2016, Guideline n. 22 (Use of data obtained from the online environment and digital tools in health related research) highlights the need for privacy protection in combination with technological capabilities. When researchers use the online environment and digital tools to obtain data for health related research they should assess the privacy risks of their research, mitigate these risks as much as possible and describe the remaining risks in the research protocol. The development of regulations and codes to allow for the widespread, lawful, ethical and secure use of IT in research consent should be supported (Taber C. et al, 2016).
c) Furthermore, technology evolves constantly and available tools change continuously and keeping track of progress and available tools is challenging. Although smartphone use and familiarity with mobile technology are growing, they are certainly not evenly distributed across populations (Grady, 2017). Scientific literature shows that in the African context, experiences with integrating ICT in action-oriented and cross-cultural communication projects

have been developed later and more slowly than in high-income countries (Larsen N. et al. 2014). A digital divide means that unequal access to digital technologies as well as highly divergent levels of online literacy persist (EGE Opinion No. 29 2015; NBC 2006).

d) Even more of an ethical challenge is the inability of a part of population to participate in smartphone-based research studies because of issues related to access or cost of smartphones or data connectivity. Another issue concerns access to technologies. There is, today, a "digital divide" because of many factors, such as a socio-economic gap and the network coverage for the Internet in the area under consideration (NBC 2015). Equal access should be guaranteed, allowing everyone to acquire tools, knowledge, skills to use new information technologies, according to the principle of equality, equal opportunities and non-discrimination (NBC 2016).

4. Recommendations

1. Researchers should identify and address:

a) social and economic vulnerabilities which may interfere with the self-determination of individuals and which may lead to an inadequate risk awareness;
b) coercion: avoiding social conditioning, threats, or pressures by the research team
c) undue influence: respect for free and informed consent acknowledges that potential research participants must not be unduly influenced by use of inducements (i.e. through financial benefits or offering better healthcare).

2. An intercultural approach to communication should be adopted in all cases where there is cultural diversity between the research team and prospective research participants, insofar as this diversity becomes challenging in terms of communication effectiveness and affects the latter's autonomous decision-making throughout the entire informed consent process (before, during, and after the end of a clinical study, in the sense of having the proper information to be able to decide whether to participate in a clinical study, stay in or leave the study at any time without any form of retaliation), an adequate understanding of what is at stake, in terms of benefits (avoiding misunderstandings and misconceptions related to an overestimation of envisaged benefits, e.g. the so-called "therapeutic misconception") and risks (avoiding an underestimation of potential risks, i.e. due to the expectation of receiving health services in the context of public health systems with severe resource constraints), as well as of required behaviours after the end of the study to protect participants' health.
   In particular, an intercultural approach to communication should involve the following strategies:

a) to overcome stereotypical thinking and a "one for all" communication method, devoting attention to the cultural backgrounds of patients or research participants and to the specific conditions of individuals belonging to the same culture, contributing to achieving a more respectful, complete and effective informed consent process. Anything in the nature of the research which the participant may find morally or culturally sensitive should entail some corresponding sensitivity in obtaining consent;
b) to adapt and tailor the ways of conveying information. Information should be given in a culturally appropriate way, relying on cultural mediators;
c) to facilitate potential participants' comprehension through previous consultation with cultural insiders and local representatives regarding the most effective ways of communicating the purpose of the clinical study; investigators might consider conducting focus groups with representatives of population groups who may be recruited to a clinical study in order to understand issues and concerns associated with preparing the consent form and developing approaches to obtaining consent;
d) to safeguard the understanding of the nature and the implications of the research, including sufficient time and a proper environment for subjects to consider their participation and discuss it with family and friends; provision of adequate information about what the clinical study entails, also in terms of burdens (with regard to research in general and the specific research in particular);
e) to foster a trust relationship between the researcher and the prospective participant, ensuring respect for the cultural and religious values that shape his/her identity through a participant-centred approach to communication (taking into account the needs and preferences of research subjects), alongside building long-term relationships between the community and the research team. This could help to overcome false perceptions of exploitation in participants.

3. An active community engagement is recommended in order to fulfil ethical requirements. The following strategies can be devised:

a) the inclusion of members of the community involved in the clinical study in the Institutional Review Board, in order to include community views and perspectives in the ethical review of the study;
b) to build long-term, mutually beneficial relationships between the community and the research team, to be applied before, during and after research studies with different strategies according to different phases of the research study, for example: engaging in full and frank discussions about the potential benefits and harms that the participants and the community might encounter; ensuring the alignment of the research to local needs; paying due attention to the impact of the study and the study team upon the participants, their families, the local community and the environment; taking sufficient time to ensure that the implications of the study have been fully understood by participants and the community;
c) consultation with community members, in particular on how to work with the community, e.g. providing a forum for discussing and addressing issues arising from participants and community representatives; carrying out an ongoing "dialogue" between researchers and the community about the proposed study and its potential implications, or a more structured consultation that would take into account the concerns of a community or a socially identifiable group; consultation initiatives on information materials;
d) periodical meetings with local health teams to inform them of potential studies, including meeting in the local languages with the key leaders in the community including the village head, the religious leaders; community feedback meetings at the end of the trials can also be useful to inform participants about the end of a study and share study results;

4. For an interculturally-sensitive informed consent, the informed consent procedures should adopt a personalized approach to achieve genuine understanding. In addition to community consultation and other community engagement strategies (see n°. 3), aimed at verifying that informed consent takes into account cultural practices, the following elements should be included in the informed consent process:

a) the process of "back-translation" of the informed consent form (after the translation of the consent form in another language, the form is then given to a native speaker who translates the document back to the original language), devoting particular attention to the appropriate use of local dialects and terminology that effectively communicates the meanings of words to potential research participants;
b) pre-testing consent forms with individuals from the study population;
c) with some populations, where the language is generally spoken and not written, the possibility to read the document in English but discuss it in the local language;
d) using visual tools, such as creating small video clips where a community member explains the research and the consent process in their mother tongue.

5. Researchers should make sure that women with particular vulnerabilities deriving from the intersection of gender, ethnicity, socio-economic factors (i.e. dependence on hierarchical structures, low-income status), culturally different from the research team, and with low literacy levels, have fully understood all benefits and risks related to clinical research enrolment and freely consented to participate. The possibility of cultural intermediation with a gender approach should be considered, in order to bridge communication gaps.

6. Intercultural communication strategies with a gender perspective should include:

a) health communication programs tailored to needs, roles, and interests of women and men from diverse cultural backgrounds (taking into account spousal communication and power dynamics between men and women, decision-making processes, social and cultural constraints and opportunities);
b) communication initiatives aimed at assessing potential positive and negative program impacts and communication capacity (i.e. access to media for women and men and their media habits in different cultural groups: in particular, identifying which communication channels, radio, tv, print, talks, community meetings, are used by women/men for health information and how this differs according to gender, culture, health literacy levels);
c) making sure that practices and use of selected media do not reinforce gender stereotypes;
d) pretesting and re-testing messages, concepts, and intended program formats with women and men separately to identify gender-based suitable solutions. These materials should be tailored to the different cultural groups they are addressed to.
e) assessing whether reliance on social networking sites (i.e. Facebook) with regard to enrolment communication initiatives, may expand geographic reach of target populations from diverse cultural backgrounds, while maintaining confidentiality on participation procedures and adequately protecting personal data.
f) involving culturally-competent and language concordant female members of research teams to avoid breaching cultural sensitivities about gender interactions.
g) improving informed consent of culturally-diverse women through the use of multimedia tools (i.e. computerized, audio questionnaire to assess participants' comprehension of informed consent; testing the acceptability and ease of digital tools in focus groups with culturally-diverse women; developing gender-tailored educational videos to empower potential participants during the informed consent process.

7. In the case of clinical research with fertile or pregnant women from diverse cultural backgrounds, a culturally-sensitive informed consent should tailor the communication of potential benefits and any possible risks (specifying the extent, envisaged or potential) for embryos and foetuses to the culturally diverse women involved: a fertile woman should be aware and fully informed of methods to avoid pregnancy before, during and after the clinical study (the period of risk is to be defined and communicated according to the type of study). This information should be clearly provided by the researcher, respecting the woman's choices and moral or religious convictions. A culturally-sensitive communication on contraception and participation requirements for fertile women should also include the possibility of abstention from sexual intercourse, whenever the requirement of specific contraceptive methods clashes with personal behaviours based on religious beliefs, which could ultimately lead to women of particular religious groups' reluctance to participate in clinical research.

8. Fertile, pregnant or breastfeeding women from diverse cultural backgrounds should be able to involve their partners in the informed consent process, whenever they feel the need to consult with them, but insofar as the woman's autonomy and decision-making is protected with regard to research participation. The degree of involvement of partners may be adapted to participation risks and requires the elaboration of adequate criteria, which need to be explicitly mentioned before enrolment.

9. Intercultural communication strategies aimed at pregnant women in clinical research should focus on:

a) the possibility to rely on face-to face interactions with health providers and the research team throughout the entire informed consent process, in order to overcome any possible culturally-based communication barriers and manage pregnancy-related concerns.

b) community engagement strategies, including focus groups among pregnant women to identify key communication barriers to research participation (i.e. relying on targeted messages and culturally-sensitive materials with a gender perspective, as well as community-based participatory research methods).

c) accommodation of time constraints of pregnant women by taking advantage of mobile technology (e.g. this would allow researchers to educate participants on the clinical study without taking additional time out of pregnant women's schedules, and therefore reducing time burden of research participation).

d) the possibility to follow-up on study results with their clinician, especially given pregnant women's particularly vulnerable physiological condition (this could contribute to building trust in the research team)

10. A cultural competence training for researchers would guarantee an effective communication with participants from diverse cultural and religious backgrounds during the whole research process and this interaction could contribute to improving access to participation of people from diverse cultural backgrounds in research. The cultural competence of researchers should be developed through appropriate strategies, such as:

a) an adequate education of researchers, also through transcultural medicine;

b) the building of a bond of trust between researchers and prospective participants;

c) involving cultural mediators to create equal conditions for subjects with diverse cultural and religious backgrounds;

d) encompassing cultural insiders' engagement to gain a deeper understanding of the sociocultural contexts of specific population groups or the research setting.

11. In order to facilitate understanding of research methods within culturally-tailored practices, an appropriate assessment of the possible use of digital tools in the informed consent process can be carried out. Using multimedia informational aids could contribute to bridging the knowledge deficit about research and guarantee an information tailored to persons of diverse health literacy levels and of all backgrounds. It is possible to evaluate the following digital-based strategies:

a) envisaging digital platforms including interculturally-tailored audio-visual interventions, animations and interactive tools to improve the informed consent process. These tools can be assessed by engaging cultural mediators and cultural insiders during the study's preparatory stage of educational and information materials. This will ensure that the selection of images and communication methods is truly effective, does not clash with cultural values, fuel or lead to distorted health perceptions in the cultural groups involved, or reinforce power differentials in promoting messages that could be misinterpreted as communicating a necessary duty to participate in the clinical study, instead of empowering subjects to make their own autonomous decision, which entails both options to accept or refuse enrolment. The ultimate goal of relying on digital tools must be the subject's empowerment with regard to clinical research, ensuring an effective and personalized approach to communication, alongside protecting privacy issues related to participation.

b) E-technology-based interventions (ICT, apps and social media) can be assessed as alternatives to the conventional informed consent in intercultural settings, in order to improve the efficiency of clinical trials and the quality of the consent process. If researchers use the online environment and digital tools to collect and manipulate data for health related research they should assess the privacy risks of their research, mitigate these risks as much as possible and describe the remaining risks in ways that are understandable to the population groups involved, taking into account cultural patterns which may influence perceptions of privacy issues.

c) Challenges stemming from the use of e-technologies could be overcome through an appropriate regulation of Information Technologies applied to informed consent to ensure their safety and effectiveness and to avoid privacy violations of people enrolled in research.

d) Before planning a clinical study using specific ICT tools (i.e. mobile technologies), it is important to identify and conduct necessary pilot studies with sites, involving representatives of the participant population. As mobile technologies can change the way sites and participants interact during a clinical study, it is essential to consider whether these possible changes in communication modes could be acceptable for the cultural groups included in the study.

e) When assessing the possibility of using ICT tools, one should take into account the fact that they are not evenly distributed across populations. The existing "digital divide" between different countries of the world is linked to many factors, such as socio-economic gaps and issues related to access to the Internet network coverage. Equal access should be guaranteed with regard to tools, knowledge, skills to use new information technologies, according to the principles of equality and non-discrimination, as well as the principle of justice in taking advantage of new opportunities to conduct research and benefiting from progress in the health field.

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