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

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#### Socio-cultural, psychological and behavioural perspectives toward informed consent process

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

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## Document Information

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## Revision History

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## Executive Summary

Task 1.7 is based on the collaborative effort of two partners of the i-CONSENT consortium (SYN and GSK). Its overarching aim is to review the literature on socio-cultural and psychological perspectives relevant to the informed consent process and participation in clinical research.

The informed consent process is complex and dependent on several factors that can determine its quality and validity. It is fundamentally a *social process* which involves multiple layers of exposure to, and processing of, information, based on written materials, formal and informal interactions, and the exchange of non-verbal communication cues.

This report draws out a number of important points about socio-cultural and psychological factors relevant to informed consent processes and participation in clinical research. At root, perhaps the central ideas are: (a) that researchers should be constantly alert and sensitive to social and cultural factors which could potentially influence the quality of informed consent they are able to obtain; and (b) that psychological factors, which may derive from the context and way in which information and decisions are presented, and which may include so-called “therapeutic misconceptions” and unrealistic expectations, are also important in determining quality of informed consent.

These two main observations are expanded upon at length in the sections that follow, based on extensive literature reviews.

## Table of main results

Number	Short Description	Reference Page
1	Researchers should be constantly alert and sensitive to social and cultural factors which could potentially influence the quality of information exchange with potential research participants.	14-15
2	Inadequate representation of individuals from different ethnic, racial or socioeconomic backgrounds is now recognised as an important concern to be addressed in the design of methodologically sound, scientifically valid research.	15
3	Up until the end of the 20th century, medical research and clinical studies were often characterised by a monocultural approach, which carried the implicit assumption of Western cultural primacy. The internationalisation of clinical research has provided the foundations for a deeper reflection on the ethical framework for clinical research in general, and for the informed consent process in particular.	16-17
4	There is evidence to suggest that, in non-Western societies, community leaders and/or family members can have a prominent role, and can have significant influence in determining whether a participant takes part in biomedical research.	17
5	CIOMS (2016) Guideline 9 (Access to populations) provides comprehensive support to researchers in overcoming cultural and linguistic barriers to obtaining genuine informed consent.	17
6	While <i>community consent</i> has become widely accepted as a norm, this approving assessment is not universal.	18
7	If we think of autonomy as a function of established beliefs, traditions and practices within a culture or community, then in modern societies, where cultural and linguistic diversity are increasingly the norm, we should expect to see a diversity of interpretations and expressions of autonomy.	19
8	Community dynamics and power relations are an important factor when approaching cultural differences in the consent process.	20
9	A lack of understanding of a culture can constitute a serious methodological barrier to sound scientific research.	22
10	In recent decades there has been particular focus on the development of approaches that overcome culture-specific barriers to the participation of research participants from minority ethnic backgrounds.	22
11	Self-awareness, cultural knowledge, and skills to foster culturally-	23



	effective and ethical communication with people of various cultural backgrounds, are fundamental elements for cultural competence.	
12	Expressions of “fear” about different aspects of clinical research point to a subconscious level, inaccessible to standard forms of information disclosure used by research teams.	26-27
13	The issue of trust (or rather <i>mistrust</i> , which can also manifest as fear or unease about certain aspects of research) emerges as a critical determinant of better representation of all groups in society.	27-28
14	Culture and language are intimately intertwined. So the use of translated informed consent materials can be pointless unless information is explained by someone who fully understands the culture and concerns (not just the language) of the potential participants.	30
15	Where possible, researchers should consult with local ethics review bodies or community stakeholders when conducting research cross-culturally.	34
16	While researchers want to ensure their subjects are “informed” about the nature, responsibilities, rights and effects of research, so researchers should make sure <i>they</i> are “informed” about the cultural contexts of the places where they work, and should make efforts to adapt to these contexts where appropriate.	35
17	Factors increasing satisfaction with the informed consent process in clinical trials include: <ul style="list-style-type: none"> <li>● Easy to read and understanding of informed consent document, with lower consent anxiety.</li> <li>● Investigator communication training: good discussion.</li> <li>● Appropriate treatment information, where patients feel their voluntariness and ability to decide.</li> <li>● Physician being friendly and dedicated, encouraging questions to patients and also the presence of family and nurses.</li> <li>● Positive language on the information presented.</li> <li>● Enough time to think the decision.</li> </ul>	43
18	Factors decreasing satisfaction with the informed consent process in clinical trials include: <ul style="list-style-type: none"> <li>● Not enough time to deliberate.</li> <li>● Investigator language and structure of the consultation, pressured by the trial.</li> <li>● Making a decision was anxious for patients, who are sometimes subject to an information overload.</li> </ul>	43

	<ul style="list-style-type: none"> <li>● The whole process being too rushed.</li> <li>● Long leaflets and being left alone reading it without the immediate opportunity to ask questions.</li> </ul>	
19	Pregnant women are a vulnerable group very underrepresented in clinical research. Understanding the barriers and challenges for retention of this population would help to advance in prevention and treatment options for them.	44
20	There are examples where subjects decide to withdraw from the study when they are asked to re-consent, or re-sign a form. Institutional Review Boards (IRBs) should be the organisms that decide whether the re-consent is necessary.	49
21	Every measure and effort should be made by the researchers to detect whether any therapeutic misconceptions exist for the person that enrolls for a clinical trial.	52
22	To raise the quality of informed consent, it is fundamental for researchers to consider and assess various factors that can contribute to optimistic bias, such as past experiences and perceived controllability.	54

## 1. Introduction

The present report has been prepared in the scope of WP1: *A multi-layered approach to informed consent*. The scope of this WP entails a wide spectrum of areas of study in relation to informed consent in the context of clinical research. This comprehensive exercise will lay out the foundations for the development of improved and tailored strategies in relation to the informed consent process (WP2) and provide the necessary input for the development of innovative guidelines for informed consent, under a gender perspective (WP3).

Task 1.7 is based on the collaborative effort of two partners of the i-CONSENT consortium (SYN [sections 1-3, 4.4-4.6] and GSK [sections 4.1-4.3]). Its overarching aim is to review the literature on socio-cultural and psychological perspectives relevant to the informed consent process and participation in clinical research.

This comprehensive study was carried out as a narrative review, based on a consistent and systematic approach. The methodology is described in **section 2**.

Cultural diversity in Europe has been influential in many respects. It has certainly extended the discourse surrounding conditions, parameters, and requirements for ethical conduct of clinical research. The informed consent process is complex and dependent on several factors that can determine its quality and validity. Rather than being a one-off, temporally delimited event, informed consent exchanges represent a continuous and dynamic process that unfolds across different phases of a research study. It is fundamentally a *social process* which involves multiple layers of exposure to, and processing of, information, based on written materials, formal and informal interactions, and the exchange of non-verbal communication cues.

The socio-cultural dimension is one of the greatest challenges for the research coordination team to overcome in the context of clinical research, especially in the cases where there are time constraints and scarcity of resources. Similarly, equal representation of minority groups is critical for the scientific integrity of research, as well as for providing equal opportunities to all people who may benefit from participation in research. A systematic approach to overcoming cultural and linguistic barriers by implementation of culture-sensitive strategies during all stages of research can produce a positive impact, not only for representation, but also retention of participants enrolled to studies. In this document, **section 3** investigates socio-cultural aspects of the informed consent process.

In **section 4**, a systematic literature review, which was carried out as part of the Clinical Trials Transformation Initiative (CTTI) informed consent project, is presented. It reveals different factors associated with patient satisfaction and dissatisfaction in the informed consent process, and looks at key issues such as retention, factors affecting patient participation in clinical trials, factors affecting parental consent in paediatric clinical trials, and re-consent. Finally, the concepts of “therapeutic misconception” and “unrealistic optimism” are discussed.

## 2. Methods

Task 1.7 is based on the collaborative effort of two partners of the i-CONSENT consortium (SYN, GSK). Its overarching aim is to review the literature on socio-cultural and psychological perspectives relevant to the informed consent process and participation in clinical research.<sup>3</sup> This comprehensive study was carried out as a narrative review, based on a consistent and systematic approach to the collection of scientific evidence and available studies on the topics under investigation in the scope of this task.

### 2.1 Eligibility criteria

#### *Inclusion criteria*

Both observational and experimental studies were considered for the review. Sub-populations selected were adults, ethnic/racial groups, cultural groups, minority populations, and vulnerable populations. Eligible papers were those published in a peer-reviewed journal in English, available in full-text, from 1987 to 2017.

#### *Exclusion criteria*

Studies excluded from the review were those relevant to medical treatment and/or medical care, considering that the focal point for this task was clinical research / clinical trials.

### 2.2 Search strategy

The databases used for conducting the primary search (first wave) of scientific papers published in peer-reviewed journals were MEDLINE (PubMed), ResearchGate, and Google Scholar. A second wave of database searches for available research studies was carried out, to retrieve additional articles following the initial screening process. The Mendeley reference management tool was used to keep track of and store retrieved articles, and in a later phase to perform the article screening process.

The initial search was run on MEDLINE (PubMed), with a total of 38 different combinations of keywords and/or Medical Subject Headings (MeSH) inserted. The main subject heading used in all different combinations was “informed consent”. Table 1 provides the full list of keywords/MeSH and filters applied as part of the search strategy for scientific articles.

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<sup>3</sup> The term “*socio-cultural*” comprises various elements such as language, religion, values, standards and customs shared by members of a community or an ethnic group. The present report examines various culture-specific parameters and considerations regarding the involvement of research participants from diverse ethnic and/or racial groups, as well as the application of the concept of “autonomy” for ethnic minority populations in relation to the informed consent process. The various aspects associated with “*religion*” as a defining factor, which can influence the decision-making process in the context of informed consent, are investigated in Deliverable D1.4: *Ethical issues concerning informed consent in translational/ clinical research and vaccination*.

## 2.3 Study selection

The combined results from the initial database search returned more than 4,000 scientific articles in total, screened by *title* to identify degree of relevance for the purposes of this review. As a next step, the articles were screened by *abstract* to assess the relevance for this review. Given the broad scope of the topic under investigation, a total of 213 scientific papers were shortlisted as eligible for full text review. Discrepancies were resolved by discussion among the reviewer team. In the end, a total of 114 scientific articles were selected and analysed for the purposes of this review for the section on socio-cultural perspectives, and 23 articles for the section on the psychological perspectives (specific to the therapeutic misconceptions and unrealistic optimism).

**Table 1:** Search strategy for retrieval and selection of studies.

DATABASES	SEARCH FIELDS	SEARCH KEYWORDS	FILTERS
MEDLINE, PubMed	Title	1. "informed consent"	English
	Abstract	2. "autonom*" OR "decision-making"	Full text available
	MeSH	3. "clinical research" OR "biomedical research" OR "clinical trials as topic"	Humans
	Text	4. "culture*" OR "socio-cultural" OR "cultural characteristics" OR "cultural diversity" OR "cultural competence" 5. "belief*" OR "perception*" OR "attitude*" 6. "method*" OR "technique*" OR "strategy*" 7. "barrier*" OR "challenge*" 8. "ethnic*" OR "minorit*" OR "vulnerable populations" 9. "unrealistic optimism" OR "therapeutic misconception"	Peer-reviewed journals Publication date from 01/1987 to 12/2017 (30 years in total)

### 3. Socio-cultural perspectives and the informed consent process

This section investigates socio-cultural aspects of the informed consent process, i.e. the cultural factors pertaining to the reaction of different – often minority – groups in society to the informed consent process. The section also discusses the challenges and barriers to the participation of population groups of specific characteristics in clinical research.

As remarked in deliverable D1.1, rather than being a one-off, temporally delimited event, informed consent exchanges represent a continuous and dynamic process that unfolds across different phases of a research study. It is fundamentally a *social process* which involves multiple layers of exposure to, and processing of, information, based on written materials, formal and informal interactions, and the exchange of non-verbal communication cues. In the context of the informed consent process, the quality and effectiveness of informational exchanges on is dependent on a number of factors. These factors collectively determine the extent to which information is likely to be evaluated as *relevant* and *appropriate* to potential research participants. Manson and O’Neill (2007) highlight the following important points about informational exchanges.<sup>4</sup>

- “*Informing is context-dependent*” (Manson & O’Neill 2007: 41). What is communicated on a given occasion depends on who is speaking to whom, in which circumstances, the background knowledge or beliefs of those parties, and many other contextual features.
- “*Informing is norm-dependent*” (Manson & O’Neill 2007: 41-2). Communication depends on background ethical, epistemic, and conversational norms, as well as on a variety of societal conventions. Where there is a lack of trust between parties (due to suspicion that norms have been violated, e.g. by lying or exaggerating), fully successful communication may not be possible.
- *What is communicated often goes beyond what is literally said: it matters how you say something* (Manson & O’Neill 2007: 44). The way in which something is said, the tone of voice, gestures, body-language, and a variety of other factors convey or imply additional information beyond what is literally said by a speaker.
- *What is communicated often goes beyond what is literally said: “informing is inferentially fertile”* (Manson & O’Neill 2007: 46-7). An audience can typically make various inferences from what a speaker says. The speaker can anticipate some of these; indeed, he or she may intentionally attempt to elicit some of them. Other inferences cannot be predicted because they depend on the audience’s background knowledge or beliefs.

When misunderstanding, miscommunication, or other communicational-misfires are made more likely due to the speakers having insufficient familiarity with or understanding of their interlocutors’ cultural backgrounds, factors such as these are lent added complexity. Social

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<sup>4</sup> Further discussion of this issue is provided in deliverable D1.1.

and cultural factors are always present in any form of human communication. Researchers should therefore, be constantly alert and sensitive to social and cultural factors which could potentially influence the quality of information exchange with potential research participants. The quality of information exchange has a direct link to the ability of a potential research participant to take a genuinely informed, voluntary decision to take part in a study.

A number of empirical studies support the claims above (Sudore et al., 2006). It is thus welcome that national and international guidelines for research have attempted to mainstream the concerns by setting out provisions for the protection of vulnerable populations and respect for the needs of culturally diverse groups. These guidelines form the starting point from which this section begins.

### 3.1 International guidelines and informed consent: the socio-cultural dimension

Cultural pluralism is increasingly the norm in modern societies. According to Eurostat, a total of 4.7 million people emigrated to an EU-28 Member State in 2015, of which an estimated 2.7 million came from non-EU Member States.<sup>5</sup> Cultural diversity in Europe has been influential in many respects. It has certainly extended the discourse surrounding conditions, parameters, and requirements for ethical conduct of clinical research. To give just one instance, inadequate representation of individuals from different ethnic, racial or socioeconomic backgrounds is now recognised to be an important concern to be addressed in the design of methodologically sound, scientifically valid research.

Over the past few decades, international organisations and institutional bodies have attempted to defined standards and ethical principles for clinical research. Notable examples include the World Medical Association (WMA) *Ethical Principles for Medical Research Involving Human Subjects* (also known as the *Declaration of Helsinki of the 18th WMA General Assembly*); the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Health-Related Research Involving Human Subjects*; and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) *Guideline for Good Clinical Practice*. A common denominator of these guidelines and policies is that they are firmly rooted, conceptually and theoretically, in the Western intellectual-philosophical tradition, being based on principles such as respect for autonomy, beneficence, non-maleficence, and justice – and, of course, they theorise informed consent as a central pillar of ethical research (Emanuel et al., 2000). Different intellectual and cultural traditions may or may not give a central role to these (or similar) principles; but even in those traditions which do, there is a strong likelihood that the understanding, interpretation, and operationalisation of these (and other) principles will be different in important respects. Understanding and acting on the differences is an important

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<sup>5</sup> More information available at <[http://ec.europa.eu/eurostat/statistics-explained/index.php/Migration and migrant population statistics#Migrant population](http://ec.europa.eu/eurostat/statistics-explained/index.php/Migration_and_migrant_population_statistics#Migrant_population)>

step towards ensuring that needs of all groups in multicultural societies are met when designing informed consent processes.

### *Cultural minorities as vulnerable groups in the context of clinical research*

It was arguably only in the period following the HIV/AIDS pandemic of the early 1990s that the scientific community really began *in earnest* to address the ethical implications of the inclusion of vulnerable populations in research practices such as international field trials. This is not, of course, to suggest that such issues were never addressed before. The Belmont Report (1979), for example, draws attention to the fact that certain vulnerable groups, such as ethnic or racial minorities, may be easy to manipulate as a result of, say, their socio-economic status, and that they should be protected accordingly.

Ethnic and racial minority groups were identified as “vulnerable populations” in guidelines such as the World Health Organization (1995) Guidelines for Good Clinical Practice for Trials on Pharmaceutical Product and the ICH Steering Committee (1996) Guideline for Good Clinical Practice. The latest version of the CIOMS Guidelines (2016) specifies that ethnic and racial minorities are “among members of groups that have traditionally been considered vulnerable (Guideline 15)”. The same Guideline explains the conditions in which vulnerability can emerge: “[...] lack of access to medical care, membership in ethnic and racial minorities, or other disadvantaged or marginalized groups can be factors that constitute vulnerability”. (By contrast, the WMA Declaration of Helsinki (fifth revision, 2000) introduced a provision for the protection of vulnerable populations – though without any specific reference to ethnic or racial minority groups or to what, in general, constitutes *vulnerability*.<sup>6</sup>) The second version of the CIOMS Guidelines (1993) emphasised not only the need for wider community involvement and engagement in research, but also the need for research to be more inclusive and representative (e.g. in terms of sampling) of various sub-populations and minority groups.

This reference to *wider community engagement* and *involvement of vulnerable groups* in clinical research set the basis for the formulation of provisions in relation to the criteria for participation of ethnic and racial minority groups. This has been a positive step towards addressing the assumption that there is a universal system of ethical principles and values which governs the conduct of research and which everyone accepts. In a commentary about the cultural influences in communication and informed consent, within the wider context of updating the second version of the CIOMS Guidelines, Fernando Lolas (2002), Former Director of PAHO/WHO Regional Program on Bioethics explained that: “*The need to find ways to take account of cultural, ideological, ethnic, gender and religious differences, comes at the end of an era when the emphasis has been in the direction of attempting to find ways of transcending cultural differences to achieve universal principles binding on all, under all or most circumstances*”. Up until the end of the 20th century, medical research and clinical studies

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<sup>6</sup> For example, Article 19 indicates that “*some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.*”



were often characterised by a monocultural approach in the formulation of ethical norms and principles, which carried the implicit assumption that Western culture had primacy over others. The internationalisation of clinical research has provided the foundations for a deeper reflection on the ethical framework for clinical research in general, and for the informed consent process in particular.

### *The element of culture in the international policy framework*

There is evidence to suggest that, in non-Western societies, community leaders and/or family members can have a prominent role, and can have significant influence in determining whether a participant takes part in biomedical research (Marshall et al., 2006). This is just one indication of the ways in which it can be challenging for researchers to identify culturally appropriate and respectful means to effectively communicate the necessary information to facilitate the decision-making process for informed consent. What works in one context cannot be uncritically assumed to work in another.

Addressing these kinds of concerns, the CIOMS (2016) Guidelines provide recommendations for cross-cultural cases. Guideline 9 (Access to populations) indicates that:

*“In some circumstances, a researcher may enter a community or institution to conduct research or approach potential participants for their individual consent only after obtaining permission from an institution such as a school or a prison, or **from a community leader, a council of elders, or another designated authority**. Such institutional procedures or **cultural customs should be respected**. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent. In some populations, **the use of local languages may facilitate the communication of information** to potential participants and the ability of a researcher to ensure that individuals **truly understand the material facts**. Many people in all cultures are **unfamiliar with, or do not readily understand, scientific concepts** such as placebo or randomization. Sponsors and researchers must use **culturally appropriate ways** to communicate information necessary for adherence to the requirements of the informed consent process. They must also **describe and justify** in the research protocol the procedure they plan to use in communicating information to participants. The project must include any resources needed to ensure that informed consent can be properly obtained in **different linguistic and cultural settings**.”*

This is a comprehensive Guideline, supporting researchers in overcoming cultural and linguistic barriers to obtaining genuine informed consent.

Guideline 15 (Women) draws attention to:

*“[...] 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 (see Guideline 18 – Women as research participants)”.*

Scientific studies in, for example, Nigeria, China and India have stressed the importance of the social context in societies where family members and/or spouses have the final authority to make clinical decisions (Bhan et al., 2006; Malik, 2011; Osamor & Kass, 2012; Fan, 1997). In such contexts, theorists consider alternative conceptions of autonomy, such as “*relational autonomy*”, which suggests that a person is defined through their relationships with others, and acknowledges the emotional and embodied aspects of decision-makers (Walter & Ross, 2014), and “*harmonious dependence*”, which is an influential feature in the decision-making process in many East Asian families (Fan, 1997).

The availability of these alternative conceptions of autonomy – which is anyway a difficult concept (see deliverable D1.1 for discussion) – serves as an indication of the difficulty of developing a transcultural approach to the informed consent process.

While *community consent*, which foresees that consent is obtained through dialogue with community leaders and often does not require written agreement, has become widely accepted as a norm<sup>7</sup>, this approving assessment is not universal. The WMA (2013) Declaration of Helsinki takes a somewhat different stance in relation to the involvement of third parties in the decision-making process. Article 25 (Informed consent) specifies that

*“[...] while it **may be appropriate to consult family members or community leaders**, no individual capable of giving informed consent may be enrolled in a research study unless he or she **freely agrees**”.*

This demonstrates that there is still some level of disagreement as to the applicability of concepts such as *relational autonomy* and *community consent*, and a residual expectation in some quarters that individual autonomy cannot be overridden by, or subject to, another person’s veto or prohibition.

The UK Guidelines for Management of Global Health Trials published by the Medical Research Council (2017) also support the ideas that customs and cultural norms should be respected and that it may be inappropriate for a researcher to enter a community and directly approach participants without first obtaining permission from a community leader, council of elders, or similar. These guidelines note, however, that agreement of the community leadership may be sought prior to the consent and/or assent of individual participants, **but it cannot replace them**. Only in exceptional circumstances – where study participants represent an entire community – can it be appropriate to seek community consent without individual consent.

Article 26 (Informed consent) of the WMA (2013) Declaration of Helsinki concerns the possibility of obtaining informed consent in non-written formats. The article states:

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<sup>7</sup> See WHO Research Ethics Review Committee – The Process of Obtaining Informed Consent. [http://www.who.int/rpc/research\\_ethics/Process\\_seeking\\_IF\\_printing.pdf](http://www.who.int/rpc/research_ethics/Process_seeking_IF_printing.pdf)

*After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, **preferably in writing**. If the consent cannot be expressed in writing, the non-written consent must be **formally documented and witnessed**.*

Such an approach can be considered “*culturally-sensitive*” since the practice of obtaining written informed consent may be seen as inappropriate in some cultures (Hanrahan et al., 2015). Previous research has shown that some ethnic minority groups favour the use of verbal as opposed to written information when participating in research (Barata et al., 2006). The use of the word “*preferably*” in the guidelines leaves adequate space and options for the researcher to consider alternative methods to obtain informed consent within a framework where social norms and values are respected during all phases of the process.

The need for sensitivity toward cultural diversity is expressed in the report on Ethics of Research Related to Healthcare in Developing Countries by the Nuffield Council on Bioethics (2014), as well as the UNESCO (2015) Universal Declaration on Bioethics and Human Rights. The latter underlines the importance of being sensitive to cultural diversity without infringing upon human dignity, human rights and fundamental freedoms (Article 12). This sensitivity to cultural diversity and awareness of social determinants that may influence informed consent and the decision-making process are discussed in the next sections.

### **3.2 Autonomy and communication in high-context and low-context cultures**

The ethical principle which, in the Western tradition at least, is most generally accepted as the basis of “*informed consent*” is *respect for autonomy*. While the force and content of the concept of autonomy is subject to considerable debate, we may say that it is rooted in the basic idea that individuals should have the capacity to make decisions free from coercion and external constraints (Beauchamp & Childress, 2013; Lomelino, 2009).

In medical contexts, four core elements are thought to constitute the necessary conditions for safeguarding an individual's autonomy in informed consent:

- (a) *information disclosure* – the patient must have an adequate informational base upon which to make the decision;
- (b) *voluntariness* – the patient must be allowed to make the decision voluntarily;
- (c) *comprehension* – the patient must demonstrate an adequate level of understanding and ability to process information presented; and
- (d) *competency* – the patient must be competent to make the decision.

If we think of autonomy, comprising these four elements, as a function of established beliefs, traditions and practices within a culture or community, then in modern societies, where cultural and linguistic diversity are increasingly the norm, we should expect to see a diversity of interpretations and expressions of autonomy.

Markus and Kitayama (1991) suggest that underlying cultural philosophies and traditions have a significant influence on how members of a community conceptualise *self*, *others*, and their *inter-connectedness*, framed in a continuum of in- and inter-dependence. Independent conceptualisations of self tend to focus on unique attributes and behaviours expressed by an individual which can be disconnected from the wider socio-cultural context, interdependent conceptualisations tend to focus on the self in relation to others (Markus & Kitayama, 1991).

In communities where an interdependent conceptualisation of self exists, the notion of autonomy may not be evaluated or considered to be as important as protecting the interests and values of the community (Lomelino, 2009). Thus, the process of obtaining informed consent may be focused more around *community risk and benefit*, rather than possible consequences for individuals. In these communities, communal decision-making appears to be the norm (Krogstad et al., 2010). This may be considered an expression of *relational autonomy*, wherein the social context plays a key role in decision-making, and where it is commonly seen as appropriate that personal decisions should be taken only after the involvement of family or community members.

Article 25 (informed consent) of the Declaration of Helsinki (WMA, 2013) refers to the influential role of family members and community leaders in decision-making in the context of the informed consent process. However, it does not consider the profound impact of power relations in some cultures (at community or family level). This influence, if not addressed, can leave a person more susceptible to coercion, or veto or prohibition by another, without adequate protection from the research coordination team (Clough et al., 2013).

Since decision-making power does, in some communities, reside with family or other community members (heteronomy) to a greater extent, community dynamics and power relations are an important factor when approaching cultural differences in the consent process (Thomas, 2012). Family- or community-specific parameters must be considered in the assessment of a person's capacity to make genuinely autonomous decisions (Lomelino, 2009).

Edward T. Hall, a pioneer in anthropological research, attempted a classification of cultures based on contextual systems used for communication and processing of information. Hall (1976) argues that two types of culture exist. *Low-context cultures* emphasise independence, the individual, and a future-time orientation. *High-context cultures* emphasise interdependence, interconnections with others, and a present-time orientation.

Importantly, in high-context communication cultures (typically collectivist, non-Western type cultures), most of the information to be communicated is either available in the physical environment or supposed to be already known; hence little has to be said. In low-context communication cultures (typically individualistic, Western type cultures), the majority of information has to be directly communicated. According to Hall (1976), it is also characteristic that:

*“high context cultures make greater distinctions between insiders and outsiders than low-context cultures do. People raised in high-context systems expect more of others than do the participants in low-context systems. [...] Also, in high-context systems, people in places of authority are personally and truly (not just in theory) responsible for the actions of subordinates down to the lowest man. In low-context systems, responsibility is diffused throughout the system and difficult to pin down”*  
(p. 113)

These differences are clearly relevant to clinical research, and especially to the effort to determine how culturally diverse populations should be approached in the informed consent process. Cultural context is a critical determinant of the autonomous quality of decision-making in informed consent processes.

An important aspect of high-context communication cultures is that less information is conveyed by verbal expression, with much of a message being embedded in the social context or internalised in the communication process itself. It has also been suggested that disclosing *too much* information in a high-context communication culture may have the paradoxical effect of raising suspicion that the researcher is withholding information. Such cultural idiosyncrasies play a critical role in determining standards of information disclosure in relation to informed consent (Del Pozo & Fins, 2008). And there are further variables to be considered besides. A study in a high-context Arabic country (Saudi Arabia) revealed that norm perception of information disclosure may be age- and gender-dependent, with male, older, and more educated patients being more supportive of greater disclosure of information (Hammami et al., 2014). Overall this makes for a delicate balance of information exchange (Bowman, 2004), in which the party providing information must be sensitive to nuances of communicative style.

The question of whether to obtain *written* informed consent from participants as a standard practice in clinical research has also been explored under the prism of high-context/low-context cultures. Zahedi and Larijani (2009) have argued that, in high-context cultures, to require written consent via a signature may actually be counterproductive: a *“request to sign a written form may have a particular meaning of blurred mutual trust for the patient, especially when there is not an effective linguistic communication”* (Zahedi & Larijani, 2009: 3).

Similarly, Mertens (2012) reported that requests for a signature can be perceived as insulting if one’s word has already been given. This can undermine the entire consent process. Killawi et al. (2014) identified similar potential problems with obtaining signed, written consent, including a possibly negative association with formal transactions, the arousal of suspicion or concern, the potential of difficulties for illiterate persons, or the implication of a lack of trust.

As noted above, the Declaration of Helsinki (WMA, 2013) specifies that informed consent should be given “[...] *preferably in writing*” (Article 25). This means that research coordination teams can be relatively flexible in their approach toward obtaining informed consent. When appropriate, written consent can be obtained. But in other cases, non-written consent can be

gathered. A waiver of written informed consent may be appropriate in certain settings (LeBaron et al., 2015), with diligent documentation of verbal informed consent that is re-confirmed throughout the study period. If the participant agrees, this process should be recorded (video or audio). If the participant does not agree to this recording, or if this is not possible, then the process should ideally be witnessed by a second member of the research team.

### 3.3 Applying cultural competence in research

A lack of understanding of a culture can constitute a serious methodological barrier to sound scientific research which can undermine the validity of a study. In recent decades there has been particular focus on the development of approaches that overcome culture-specific barriers to the participation of research participants from minority ethnic backgrounds. From these initiatives has emerged and evolved the notion of *cultural competence*.

The *NASW standards for cultural competence in social work practice* (National Association of Social Workers, 2001) define cultural competence as a process of improving individuals' and systems' ability to respond to "[...] *people of all cultures, languages, classes, races, ethnic backgrounds, religions and other diversity factors in a manner that recognises, affirms, and values the worth of individuals, families and communities and protects and preserves the dignity of each*" (p. 11).

In the healthcare context, 'cultural competence' has been defined as a concept that entails (Betancourt et al., 2003):

- (a) understanding the importance of social and cultural influences on patients' health beliefs and behaviours;
- (b) considering how these factors interact at multiple levels of the health care delivery system; and:
- (c) devising interventions that take these issues into account to ensure quality healthcare delivery to diverse patient populations.

In a paper published by Cross et al. (1989), "*cultural competence*" is described as part of a continuum, which includes multiple levels, from "*cultural destructiveness*" at one extreme to "*cultural proficiency*" at the other. These different levels and short descriptions are illustrated below:

1. **Destructiveness.** Devalue differences of cultures and apply policies, attitudes, or practices that adversely affect various populations.
2. **Incapacity.** Make biased decisions for people of other cultures and perpetuate stereotypes.
3. **Blindness.** Take a "one-size-fits-all" approach in research, and believe that if a system works, all people will be served with equal effectiveness.

4. **Pre-competence.** Desire to deliver high quality services and committed to civil rights. May feel one change in system is adequate.
5. **Competency.** Accept and respect differences. Continuously self-assess and expand cultural knowledge resources.
6. **Proficiency.** Hold culture in high esteem. Incorporate culture into leadership, research, projects, new approaches to care, and publications.

It has been pointed out by Chettih (2012) that some definitions fail to address the influence of the provider's own belief and value systems, as well as the institutional and societal factors at play. Preferable in this respect, then, are the positions of authors such as Surbone (2010), who argues that culturally competent physicians are those with the cultural awareness and cultural proficiency to deal in the most effective way with patients and research participants from diverse ethno-cultural backgrounds. According to McDonald (2009), self-awareness, cultural knowledge, and skills to foster culturally-effective and ethical communication with people of various cultural backgrounds, are fundamental elements for cultural competence. For Kohli et al. (2010: 257), "[...] *cultural competence begins with an awareness of one's own cultural beliefs and practices, and the recognition that others believe in different truths/realities than one's own. It also implies that there is more than one way of doing the same thing in a right manner*". A culturally competent researcher will actively develop and practice appropriate, relevant, and sensitive strategies and skills in working with individuals from different cultures (Cronin & Ward, 2004).

The concept of cultural competence applies also in clinical or biomedical research. Previous health research has often excluded individuals from minority ethnic backgrounds due to perceived cultural and communication difficulties. As stated by Noah (2003: 224), "*for reasons of scientific and practical convenience, minority groups were commonly excluded from clinical trials until the mid-1990s*". And even in present times, under-representation of culturally diverse populations continues to be an issue (Garza et al. 2017).

Sometimes, there might be language or literacy problems that make it more difficult to obtain informed consent. Braunstein et al. (2008) recorded some of the main reasons reported in their study for the exclusion of minority groups in clinical trials as including "[...] *the difficulty of recruitment and retention, a general belief that racial populations are essentially monolithic, without significant differences, and the desire and need to focus on optimising internal validity*" (p. 1345). Moreover, it is certainly true that explaining relatively complex or technical concepts, such as *early-phase trials*, and discussing them with *any* patients can be difficult – hence it is understandable (if not acceptable) that clinicians may take shortcuts with culturally and linguistically diverse patients (Surbone & Kagawa-Singer, 2013).

McDonald (2009) argues that stereotypes and beliefs or pre-dispositions about certain communities create barriers to their participation in research. For instance, assumptions that specific groups will be "*difficult*" or "*hard-to-reach*" will, from the research design phase, create and institute obstacles to the recruitment of participants from certain backgrounds.

Characterising such populations or minority groups as “hard-to-reach” may, in effect, also characterise them as “easy-to-ignore”. Brown and Scullion (2010) argue that the “hard-to-reach” designation is a sign of researchers’ failure to understand what the most appropriate and culturally sensitive strategies could be to approach those individuals who represent an ethnic or racial minority group. This essentially represents lack of cultural competence on the part of the researcher. Cultural self-awareness is thus essential.

Cultural competence is important for both recruitment and retention of participants and constitutes a key factor which can determine the level of success of a clinical study (Taylor, 2003). Otado et al. (2015) explored the relevance and effectiveness of applying culturally competent strategies for recruitment and retention of African American populations in clinical trials. According to them, the single most effective method for recruitment of participants was an approach which involved “[...] *going out into communities, working with people in communities and establishing relationships with hopes to build trust among those who might be potential study participants*” (p. 463). For the retention of participants, the most effective strategies included the cultivation of some form of rapport with participants, post-visit telephone calls to inquire about participants’ well-being and any concerns in relation to the studies, offering fair compensation to participants per follow-up visit, and demonstrating respect toward norms and traditions in the local community. The key element and common denominator across these methods is the effort to establish a relationship of trust with participants, and to alleviate fears and misconceptions about clinical research and medical researchers. The most prominent example feeding fears in the African American community is the Tuskegee Study<sup>8</sup>. This has been registered in the collective memory of African Americans as a case of racial mistreatment and exploitation (Otado et al., 2015; Shavers et al., 2002).

Studies have highlighted the importance of collaborative work and engagement of community members in research, this can promote the empowerment of ethnic minority groups and populations at risk of marginalisation, discrimination or stigmatisation (Oden et al, 2011). This observation is reflected in the CIOMS (2016) Guidelines on community engagement:

*“[...] Engaging the community at the earliest stage promotes smooth study functioning and contributes to the community’s capacity to understand the*

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<sup>8</sup> A study by S. C. Thomas (2012) offers the following account of the Tuskegee study, based on multiple sources collected. “*The Tuskegee study is one of the best-known examples of abuse in clinical research. The study was held at the Tuskegee Institute of Macon County, Alabama, an area known as the “Black Belt” because of its rich soil and vast number of black sharecroppers who were the economic backbone of the region. The Tuskegee study ran from 1932 through 1972. Formally called “Tuskegee Study of Untreated Syphilis in the Negro Male”, the purpose of the study was to observe the “natural history of syphilis in blacks”. The study included a total of 600 men: “400 [already] syphilitic men ...[and] 200 uninfected men who served as controls. Researchers offered multiple incentives to the participants. However, participants were misled about the purpose of the study. From 1936 through the 1960s, reports on the study were published every four to six years. An Associated Press reported unveiled the study to the media in 1972; when the public learned of this study they were outraged. The study only ended after the story went to press. By that time, only 74 of the 600 study participants were still living, and it is estimated that as many as 100 participants died from their untreated syphilis. [...] Twenty-two years later, President Clinton issued a public apology.*”



research process. Community members should be **encouraged to raise any concerns** they may have at the outset and as the research proceeds. Failure to engage the community can **compromise the social value of the research**, as well as **threaten the recruitment and retention of participants**. Community engagement should be an **ongoing process**, with an established forum for communication between researchers and community members. This forum can facilitate the creation of educational materials, planning the necessary logistical arrangements for the conduct of the research, and providing information about the **health beliefs, cultural norms, and practices of the community**. Active engagement with community members is a **mutually educative process**, which both enables researchers to learn about communities' cultures and understanding of research-related concepts and contributes to research literacy by educating the community about key concepts critical for understanding the purpose and procedures of the research" (Guideline 7).

A systematic review by Halkoaho et al. (2015) focused on cultural aspects related to informed consent in health research. Four main themes were identified as important when designing research studies in a multicultural setting. Researchers should: be aware of the local protocols, legislation and culture; consider the individual human subject's life situation; take into account the human subject's awareness of the research protocol; and ensure sensitive recruitment. They conclude that cultural-free health research is nearly impossible, and so culturally sensitive research ethics are needed. Consequently, it is necessary to have an open discussion on culturally sensitive research ethics, which focuses on values, beliefs and practices, to ensure that respect for human dignity and protection of the autonomy of the subject providing informed consent is safeguarded (Halkoaho et al., 2015).

In sum, it is important for researchers to develop cultural competency in clinical research in order to ensure:

- effective communication with culturally diverse populations;
- the development of trusting relationships between researchers and study participants;
- proportionately balanced representation of sub-groups and minority populations in research studies;
- appropriate engagement of minorities in study design and implementation in community/population-based research.

### 3.4 Under-representation and socio-cultural barriers in clinical research

The systematic efforts to identify culturally competent strategies and interventions to improve the recruitment and retention of research participants from culturally diverse backgrounds stems from evidence in the literature about the overall under-representation of ethnic and racial minority groups in clinical research (Corbie-Smith et al., 2002; Freimuth et al., 2001; Lakes et al., 2012; Siegel et al., 2015). Efforts to increase the representativeness of

participants in health research have raised questions about the basic assumptions of the informed consent process in culturally and socio-economically diverse groups (Barata et al., 2006; Bhutta, 2004).

Equal representation in clinical research is critical for the scientific integrity of research, as well as for providing equal opportunities to all people who may benefit from participation in research. This is especially important for populations of certain physical characteristics that may suffer from certain health-related problems at a higher rate than other populations (Noah, 2003). A systematic review carried out by Kwiatkowski et al. (2013) compared the proportion of under-represented minority participants in Phase III cancer treatment and prevention clinical trials conducted in the US between the periods 1990-2000 and 2001-2010. It found that there is a growing tendency for research conducted in multicultural societies to have inadequate representation of populations from diverse socio-cultural, ethnic or racial backgrounds.

Informed consent processes, and clinical research in general, need to become more culturally-sensitive. Efforts should be focused on how to be more responsive to the principles, beliefs, attitudes, norms and other socio-cultural factors that legitimately vary within culturally heterogeneous populations or societies. There is evidence in the literature to suggest that ethnic minorities express interest and willingness to participate in clinical research, hence researchers need to explore their own biases to determine why there is a relative exclusion of ethnic or racial groups from clinical research (Quinn et al., 2012). Strategies to develop cultural competence in research might include providing training on:

- the recruitment of racial and ethnic minorities;
- the consideration of contextual factors such as attitudes toward informed consent;
- addressing participants' concerns in a timely and effective manner;
- effective, culturally-sensitive ways of disclosing information, as well as the type of information disclosed.

These, and the like, could have a positive effect on the development of recruitment and retention strategies in the future (Quinn et al., 2012). On the other hand, failure to act on them could create barriers and reduce participation by ethnic and racial minority populations in research.

There are several barriers to the recruitment of culturally diverse populations in the pre-enrolment phase of research, which constitutes the initial step in the informed consent process. A systematic review by Schmotzer (2012) aimed to explore the most common barriers and provide an explanation for the low-participation rate of minorities and women in clinical studies. The most common themes that emerged as factors included:

- (a) fear associated with the randomisation process, due to lack of understanding of what the process entails;
- (b) fear of the concept of experimentation;

- (c) lack of trust toward the medical community, in particular mistrust toward researchers and sponsoring agencies (as opposed to physicians and nurses);
- (d) fear associated with a perceived loss of privacy or lack of confidentiality.

(See also: Jones et al., 2006; Mills et al., 2006; Madsen et al., 2002). These expressions of “fear” about different aspects of clinical research are noteworthy. They point to a subconscious level inaccessible to standard form of information disclosure used by research teams. It should be noted that fears about clinical experimentation have also been expressed by parents from different ethnic and racial minority groups, who had to decide about the involvement of their children in research studies (Svensson et al., 2012) (though this should be considered alongside an overall tendency of parents from all backgrounds to be more reserved regarding consent for their children’s participation in research as compared to their own participation).

In a study by Shavers et al. (2002), it was reported that the majority of African American participants expressed open disbelief concerning the purported benefits of research, and a view that most of the risks are traditionally borne by minorities. Indeed a number of studies have shown that the decisions of individuals from diverse ethnic or racial backgrounds to refuse participation in a research study are influenced by low levels of trust expressed for the healthcare system, sponsoring agencies and researchers (Brown et al., 2013; Corbie-Smith et al., 2002; Freimuth et al., 2001; Killien et al., 2000; Otado et al, 2015; Shavers et al., 2002). According to Killien et al. (2000), lack of trust and low level of understanding of the procedures are two major factors constituting a barrier to reaching culturally diverse populations in research. A further study about perceptions of participation in cancer trials among African Americans suggested that participants’ refusal to participate was due to a fear of additional burdens, and the fact that they were unable to understand various aspects of the trial (Brown et al., 2013). Other research studies with African Americans revealed that reasons of distrust arise from a legacy of mistreatment in the health care system and research abuses, where they were “*more likely to believe that someone like them would be used as a guinea pig without his or her consent*” (Corbie-Smith et al., 2002: 2459). Furthermore, the informed consent process itself was mistrusted, being perceived as a means of providing legal protection for researchers rather than a resource to improve their understanding of the research study. The study by Freimuth et al. (2001) similarly found that African Americans participating in focus groups likened the providing of informed consent to “*signing away your rights*”.

Overall, it should be taken under consideration that certain ethnic or racial minority groups may lack social integration and/or may be exposed to discrimination (implicit or explicit) by the majority-dominated society. According to Mays et al. (2007), exposure to discrimination may lead to difficulty engaging with the broader society, cultivate distrust toward elements of this society, and suspicion of healthcare systems that have historically exploited minority communities. Evidence from the abovementioned studies reiterates need for medical researchers to focus efforts on creating solid foundations to trusting relationships with

representatives from specific ethnic or racial populations or minority groups. Wright et al. (2002) emphasises the importance of involving nurses in the process, since they are usually well-informed and educated about specific trials and can provide effective communication of complex information and decrease patient anxiety about their participation. It is suggested that researchers encourage in open discourse about past abuses of minority participants and describe provisions that they have made to assure the protection of participants in their particular studies (Shavers et al., 2002). Generally, the issue of trust (or rather *mistrust*, which can also manifest as fear or unease about certain aspects of research) emerges as a critical determinant of better representation of all groups in society.

### 3.5 Linguistic challenges for diverse cultural and minority groups

A core element for the valid execution of the practice of informed consent in clinical research is the capacity to “*comprehend and process information and to reason about the consequences of one’s actions*” (Beauchamp & Childress, 2013: 114). As pointed out above, the complexity of standard protocols for informed consent in the pre-enrolment phase (e.g. from research-specific terms and concepts used) can erect linguistic and cultural barriers to participation of representatives from cultural minority groups.

There is a body of literature which suggests that participants from diverse ethnic minority groups frequently do not understand key terms, and misinterpret information provided about the level of risk (Adams et al., 2007; Criscione et al., 2003). They often mistakenly expect to receive the best available treatment despite having been “*informed*” of the randomised trial design (Joffe, et al., 2001). A systematic review of 27 studies focused on improving patient understanding of informed consent provided evidence about the difficulties with comprehension of key concepts and terms, including: *randomisation, placebo, benefits and risks* (Montalvo & Larson, 2014), and the *right to withdraw* from research participation without negative consequences (Krosin et al., 2006).

According to Hanrahan et al. (2015), an effective communication strategy – which facilitates understanding of key terms or complex concepts – can involve the use of metaphors, idioms and simple paraphrases of complex sentences. Yet attention is also drawn to the fact that extensions of meanings can result from the unintentional use of idioms or metaphors (e.g., “Don’t worry about the blood test; it’s a piece of cake”), and have connotations that are only derivable from the context in which the word is used (e.g., “the results are positive”–meaning “not good”):

“[...] *these implied connotations can relate to contextual meanings (e.g., routine expressions that only make sense in context–e.g., “what’s up?”), sociolinguistic meanings (e.g., the appropriate ways to be formal or informal), sociocultural meanings (e.g., appropriate ways to be polite in a particular culture), and psychological meanings (e.g., appropriate ways to encode attitude, emotionality, tone, stance)*” (Hanrahan et al. 2015:14).

In this area, discussion typically revolves around the necessity of making information available in different languages. This is directly aimed at overcoming linguistic barriers, but should (perhaps less directly) address health-literacy barriers.

Some studies highlight the importance of accommodating the needs of ethnic minority or culturally diverse populations by having informed consent materials translated by, and discussed with, trained interpreters (Adams et al., 2007; Eder et al., 2007). Fundamental semantic concepts in one language do not always have simple one-to-one counterparts in another. Rather, the meaning of words, phrases and sentences in two languages may be similar in some respects, and vary in others. According to Harnahan et al. (2015: 14), “[...] *consent forms may require translations of words that are not typically used in conversation, and can be awkward and/or difficult for potential subjects to understand. Also, typical of scientific language, consent forms contain numerous examples of noun compounds, consisting of two or more nouns in sequence (e.g., “substitution treatment”, “drug treatment research study”), that have no exact equivalent in many other languages, and thus often need to be rephrased (e.g., “an investigation of the use of drugs as a treatment for disease”).* A study with representatives from an indigenous group in the US (Navajo population), pointed to the difficulty of having direct word-for-word translation in informed consent documents, with several sections of the document having been worded awkwardly to convey the exact meaning in English (McCabe et al., 2005). Due to complexities of the Navajo language, when the translated version of the document was presented, an array of cultural issues arose and the interpreters often had to re-explain the meaning of some parts before the document was accepted.

Hanrahan et al. (2015) state that human communication involves micro-level socio-linguistic features concerning when to speak and not to speak, what to say and to whom, when, where, in what manner: *“The meaning of a particular word, for instance, may depend to a large degree on the context of other words. Language itself can in fact shape concepts that cannot be easily or well-translated from one language to another due to nuances, causing awkwardness. For example, one can say in English “take blood” or “draw blood” to express “the extraction of a sample of blood.” In Spanish, however, it would be quite odd for someone to say necesito tomar sangre (“I need to take blood”) since tomar is typically used to mean “drink” with liquids. The extraction of blood in Spanish is more accurately expressed by extraer (“extract”) or more familiarly by sacar (“take out”). Also, a Spanish-speaking physician would also probably substitute una muestra de sangre (“a blood sample”) for the generic term “blood”*” (p. 13). Failure of the translation process to account for these cross-cultural differences may result in miscommunication, or the mutual misunderstanding of intentions and abilities.

In the same spirit, recommendations from the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, state, in relation to Article 6.2 (concerning informed consent for families with different cultural backgrounds), that:

*“It is important that the language skills of the child and consenting parents/legal representative are sufficient for them to understand the provided information. **Also cultural differences may lead to misunderstandings.** Where appropriate, **a translator and/or a cultural mediator**, familiar with medical terminology, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available in the process of obtaining informed consent. A **translated informed consent form** could also be an appropriate way to provide trial related information adapted to the specific needs of families with a different cultural background”.*<sup>9</sup>

Another challenge in presenting information to culturally diverse populations can be relevant to perceptions about the body, causes or prevention of diseases and different understanding of risks and benefits. Adams et al. (2007) suggests that certain communities or ethnic groups may endorse what researchers might consider superstitious elements of belief. In their study with participants from the Tibetan Autonomous Region, there was a common belief that having a discussion about the possibility of bad outcomes in the context of presenting risks associated with the study could bring such outcomes into reality (Adams et al., 2007). In such cases it may be quite difficult to find the appropriate words or phrasings to communicate relevant information.

Much has been written about what would constitute a suitable approach for the translation of information presented about a research study (Harnahan et al., 2015). These points and recommendations lay further emphasis on the need to demonstrate cultural competence. Culture and language are intimately intertwined. So, the use of translated informed consent materials can be pointless unless information is explained by someone who fully understands the culture and concerns (not just the language) of the potential participants.

### 3.6 Cross-cultural perspectives from African and Asian countries

Having discussed various socio-cultural perspectives and parameters that can influence the informed consent process, this section reports on evidence about factors that determine the framework for decision-making in specific high-context cultures: India, Pakistan, Nigeria, Kenya, and China. Note that these countries are not chosen systematically for present purposes, but simply reflect those regions discussed in the literature that was reviewed.

#### India

The importance of family involvement in India is manifested in all aspects of life. Most individuals will not agree to participate in research – or even to major clinical procedures –

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<sup>9</sup> EC (2017). *Ethical considerations for clinical trials on medicinal products conducted with minors*. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (Revision 1). 18.02.2017. Available at [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017\\_09\\_18\\_ethical\\_considerations\\_with\\_minors.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_considerations_with_minors.pdf)

without first discussing it with one or more members of their family. According to Bhan et al. (2006), a researcher in India must be aware that Indian patients or research participants may prefer to involve their families or communities in the consent process in addition to giving individual consent. Gender differences have also implications for decision-making procedures, as women sometimes do not feel empowered enough to agree to participate in research until they obtain the permission of their spouses.

A study by DeCosta et al. (2004) reported that a majority of study participants relied on discussion with other community members in making decisions regarding participation in clinical trials. The study also highlighted the issue of diminished autonomy and a tendency toward paternalistic doctor-patient relationships. Patients demonstrated considerable levels of implicit trust in the medical system, and also a certain level of ignorance about the information that should be known before consenting to be a part of a research study.

According to Nijhawan et al. (2013), these factors increase researchers' responsibilities to obtain informed consent. In such contexts, the informed consent process may require additional time to allow potential participants to discuss the information presented with family or community members.

### Pakistan

A study by Malik (2011) in Pakistan investigated socio-cultural factors that affecting comprehension and decision-making as part of the consent process for research participants. Similarly to findings from Indian studies, Malik explains that, in Pakistani society, health professionals enjoy privileged positions; they are respected and highly trusted, playing a pivotal role in health-related decisions (patients may, for instance, ask what their physician would do in similar circumstances).

Again similarly to India, the role of family was found to be influential in Pakistani society when important decisions arise. According to Malik, it is common practice in Pakistan to reach a decision after "*talking to the family*", with the opinion of the head of the family often prevailing.

Although from a psychological perspective this "*dependency*" on family can be beneficial for individuals, especially in circumstances where the participant or patient is under stress or undecided about whether to enrol in research, this form of heteronymous decision making (i.e. decisions significantly influenced by others) may compromise a patient's best interest (and rights). Malik suggests that during consultations, while engaging with the family, it is essential for researcher/physician to encourage patients to talk about their values and involve them in the decision-making process, so they become more open and active as participants, rather than keeping a profile of passive recipients of decisions made by others (Hill et al. 2008).

## Nigeria

Osamor and Kass (2012) studied a traditional Nigerian community. Their aim was to identify factors that motivate people to participate in biomedical research and assess the extent to which participants involve others in the decision-making process. With regard to the motivating factors, 67% of respondents reported that they wanted to know more about their illness, 30% wanted medical care, 22% said they participated because they were invited. No significant difference was found in responses by men and women. These results are in line with the study by DeCosta et al (2004), which reported that altruism was the most common motivating factor for participating in community-based research studies.

Regarding the involvement of others in the decision-making process, over three quarters of the respondents said they talked with someone else before deciding to participate in the research study. 58% of them talked to their spouse, 29% with friends, and 23% with other family members. Only 12% talked with a health care provider. These results are similar to studies from India and Pakistan. To the question whether they had obtained permission from anyone before enrolling to the study, 39% said they did, and 61% did not. Here, gender differences were observed. These followed findings from studies in India: women were more than twice as likely as men to report that they obtained permission from someone else before participating. Nearly one-half of women obtained permission from their husbands, while only 14% of men obtained permission from their wives (Osamor & Kass, 2012).

## Kenya

In Kenya, various traditional communities organise assemblies (called “*baraza*”) which are used for both sharing information and gathering community opinions on issues of interest to the entire community, such as health-related research (Naanyu et al., 2011). In particular, these *baraza* assemblies may be useful for both research investigation purposes as well as in relation to the consent process, where relevant issues and concerns can be evaluated and discussed. In discussions among community members, understanding the benefits of research was considered a crucial component of the informed consent process.

The study by Vreeman et al. (2012) focused on how a community in western Kenya viewed participation of children in health research, and on informed consent and assent processes. Community members supported the participation of children, as research is frequently viewed as an educational opportunity for children. Most participants were opposed to asking for assent from children younger than twelve or thirteen years of age (when in some other countries obtaining assent for children aged seven and older is relatively common practice) (Wendler, 2006).

Some misconceptions emerged in relation to the involvement of children in research. Molyneux et al. (2004) suggests that many parents of children involved in studies in Kenya expected their children to benefit medically from their participation. The community endorsed parental informed consent for children’s research participation, but they also



supported having other caregivers, community leaders, and community assemblies participate in the process.

## China

A study by Wu et al. (2015), investigated attitudes toward clinical research for Chinese populations. Findings suggest that a major concern for Chinese patients from both rural and urban areas, was personal safety. Chinese patients did not attach as much importance to the information disclosed about the research, or to their freedom of choice to participate in a research study, or their right to leave the study at any time. According to Wu et al., this could be explained by considering that, similarly to Indian and Pakistani culture, the Chinese culture can be described as paternalistic and as putting more emphasis on the type of benefits for the community, and not as much about the protection of individual autonomy. Participation in a research study was largely influenced by recommendations from doctors.

### 3.7 Evidence-based recommendations

The analysis of the socio-cultural dimension in clinical research underlines the importance of a more detailed understanding of the unique local factors and parameters that influence the decision-making process for participants from particular ethnic and cultural backgrounds.

It is important to implement approaches to informed consent which can be adapted to the specificities of community groups. For instance, Osamor and Kass (2012) have suggested a “*two-stage process*” approach for individuals from cultural backgrounds where the family plays an important role in their decision to participate. The first stage comprises initial discussion with the researchers, who would also provide relevant informed consent materials to allow discussion within the family of that person. The subsequent stage (provide formal consent) would occur after the participant has consulted family and/or community members. It is also important to delineate the boundary between *consultation/discussion* and *permission*, especially in communities where such traditions and power relations exist. The researcher must be aware of whether a participant came forward as a result of an individual consultation process or whether a prior discussion and decision-making process with family or community occurred. In the latter case, the principle of autonomy may – but need not – be challenged due to possible exercise of coercion or undue influence.

The study by Quinn et al (2012) for improving informed consent with ethnic and racial minority participants concluded that the “[...] *process should include a combination of incorporating methods to increase community members’ satisfaction with effective methods for increasing comprehension of the material*” (p. 9). Such methods include taking information about the research home, having one-on-one discussions and possibly more than one meeting with researchers, and having the opportunity to discuss the issues with other study participants.

A number of considerations for adapting the informed consent process to cross-cultural settings were in the study by McCabe et al (2005). These recommendations are specific to the content and layout of the informed consent documents, based on methods which have been identified and extensively discussed in the scope of deliverable D1.1.

- Reduce strict legal and scientific jargon in the consent form.
- Restructure consent forms to reduce redundancy and repetition.
- Identify and alter, when possible, standard consent form language that may engender mistrust.
- Re-sequence the consent form to facilitate logical translations into complex languages.
- Ensure that those administering consent forms are culturally competent to address questions and potential misunderstandings.
- Specify alternative means of communication.
- Provide for community members to review and critique forms.

According to Clough et al. (2013), there are some best practices to be considered with regard to the involvement of local communities and representatives of culturally diverse groups:

- Where possible, researchers should consult with local ethics review bodies or community stakeholders when conducting research cross-culturally.
- Ethics review committees should be encouraged to assist researchers with the development of culturally sensitive ethical procedures, as well as place greater emphasis on local ethics review within the communities where the research is conducted.
- Researchers should be aware of cultural differences in the use of informed consent and other research ethics mechanisms, and discuss research methodology with local contacts.
- Researchers should design their projects to include active checks for participant understanding, as well as methods for actively seeking participant and community feedback.

Finally, to facilitate the development of more culturally sensitive plans to recruit and obtain consent from diverse communities and individuals, Lakes et al. (2012) provide a number of recommendations and questions to be considered by researchers and institutional review board members, when reviewing study plans to obtain informed consent:

- Have the researchers taken steps to understand the cultural and social contexts (including contextual factors related to race or ethnicity, language, socioeconomic status, immigration status, educational level, religion, gender, etc.) of their targeted participants that may affect interpretation or meaning of the research and informed consent process? Is that understanding reflected in plans to obtain consent for the proposed research? This understanding could be achieved in part by the examination

of existing scientific literature and empirical studies on culture, diversity and informed consent that relate directly to targeted populations or communities.

- Have researchers taken steps to build trusting relationships with participants or communities, or does their recruitment plan includes steps they will take to do so?
- Does the proposed informed consent plan encourage ongoing informed consent throughout the research process rather than simply relying on the initial consent form?
- Does the informed consent process incorporate methods of educating participants about the research process that are appropriate for that particular group of participants (e.g., oral presentations, videos showing research procedures, etc.)?
- Have the researchers considered the applicability of community or family consent as an additional step preceding individual consent?
- Has the process for informed consent (including consent forms, educational materials) been shaped by community collaboration, consultation and/or pre-tested with or reviewed by community members? Has their feedback been used to improve the process or materials? In particular, have community members been asked to identify potential risks not considered by researchers or potential assumptions (e.g., possible benefits) that should be addressed during the research education or informed consent process? Have researchers considered how increasing cultural, experiential and social diversity in participant populations could lead to additional or unexpected emotional and other risks (e.g., social stigma associated with some research results because of cultural values, traditions and beliefs) that may differ across diverse groups?
- When determining research procedures, have researchers built into the protocol reasonable accommodations or modifications that will increase access to participation for participants from underrepresented communities?

### 3.8 Concluding remarks

Efforts to cultivate a deeper sense of the cultural context within which research is conducted should begin with the assumption that *“informed”* is a concept that should travel in two directions. While researchers want to ensure their subjects are *“informed”* about the nature, responsibilities, rights and effects of research, so researchers should make sure *they* are *“informed”* about the cultural contexts of the places where they work, and should make efforts to adapt to these contexts where appropriate (Adams et al., 2007).

International guidelines and policies for the ethical conduct of research, such as the WMA (2013) Declaration of Helsinki and the CIOMS (2016) Guidelines draw attention to the need for researchers to adopt a culture-sensitive approach and accommodate the needs of participants from diverse backgrounds in which the concept of autonomy, or decision-making processes, may be different to standard practices followed in Western-type communities. Evidence from the literature suggests there is considerable under-representation of various ethnic and racial minority groups in clinical research (Corbie-Smith et al., 2002; Freimuth et

al., 2001; Lakes et al., 2012; Siegel et al., 2015). Efforts to increase the representativeness of participants in health research have raised questions about the basic assumptions of the informed consent process in culturally and socio-economically diverse groups (Barata et al., 2006; Bhutta, 2004).

Cultural competence has gained substantial ground in clinical research over the past few decades, as an approach to bridge existing communication gaps and ensure that research can be adapted to meet the social, cultural and linguistic needs of diverse ethnic and racial populations. Cultural competence is important for both recruitment and retention of participants and constitutes a key factor which can determine the level of success of a clinical study (Taylor, 2003). The systematic review by Halkoaho et al. (2015) which focused on cultural aspects related to informed consent in health research turned up four main themes as fundamental to designing research studies in a multicultural setting. Researchers should: be aware of the local protocols, legislation and culture; consider the individual human subject's life situation; take into account the human subject's awareness of the research protocol; and ensure sensitive recruitment.

The informed consent process is complex and dependent on several factors that can determine its quality and validity. The socio-cultural dimension is one of the greatest challenges for the research coordination team to overcome in the context of clinical research, especially in the cases where there are time constraints and scarcity of resources. Nevertheless, equal representation is critical for the scientific integrity of research, as well as for providing equal opportunities to all people who may benefit from participation in research. A systematic approach to overcoming cultural and linguistic barriers by implementation of culture-sensitive strategies during all stages of research can produce a positive impact, not only for representation, but also retention of participants enrolled to studies.

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## 4. Psychological perspectives to participation in clinical research

### 4.1 Factors associated with patient satisfaction and dissatisfaction on the informed consent process.

A systematic literature review that was done as part of the Clinical Trials Transformation Initiative (CTTI) informed consent project, observed different factors associated with patient satisfaction and dissatisfaction on the informed consent process. Results were obtained from 9 different countries in Europe and North America by qualitative (interviews) and quantitative (survey instruments) methodologies. In general, providing enough time to consider the decision and the informed consent form was associated with a positive factor whereas having limited time or feeling rushed and pressured was a problem (Hallinan et al., 2016).

Factors increasing satisfaction:

- Easy to read and understanding of informed consent document, with lower consent anxiety (Coyne et al., 2003).
- Investigator communication training: good discussion (Hietanen et al., 2007).
- Appropriate treatment information, where patients feel their voluntariness and ability to decide (Sørensen et al., 2004).
- Physician being friendly and dedicated, encouraging questions to patients and also the presence of family and nurses (Behrendt et al., 2010).
- Positive language on the information presented (Cox, 2002).
- Enough time to think the decision (Knifed et al., 2008).

Factors decreasing satisfaction:

- Not enough time to deliberate and being asked to consent which made feel the patient involuntarily responsible for their decision to participate (Ågård et al., 2001).
- Investigator language and structure of the consultation, pressured by the trial (Behrendt et al., 2010).
- Making a decision was anxious for patients when they were aware that the choice of participation in the study depended on them plus the informed consent document being an additional burden in relation to the amount of information that the patients had already received. These situation leads to inability to ask questions because of being so shocked by everything happening and an information overload (Cox, 2002).
- The whole process being too rushed is associated with dissatisfaction. However, in patient's situations where urgency is important, they tend to be more satisfied than upset. Also, more information available regarding the study is often claimed and taking the informed consent papers home to read is not enough (Knifed et al., 2008).
- Long leaflets and being left alone reading it without the immediate opportunity to ask questions (Locock & Smith, 2011).

## 4.2 Reasons for withdrawal

### 4.2.1 Retention

Retention refers to the process of keeping participants enrolled in the study. It consists on building a relationship with the participants that encourage them to continue in the study. Recruitment and retention are very important concerns, especially in randomized controlled trials and longitudinal studies, as they affect the validity of the research results. Failure to retain study participants may drive to invalid or inconsistent results, termination of the study before the scheduled time or exceed trial time. It has been seen that nurses are a key factor and play an important role in this process as they are an important link between patient and investigator. Some studies have found that nurses' involvement lead to a higher retention rate of the participants in a study. In this way, it is important to identify the common issues and challenges in retention, since is a threat to clinical research. Retention rates vary from 5-70%, although bias is expected when that rate exceeds 20%. When this occur, the validity of the study is altered by the reduction of the sample size and therefore, the statistical power of the study is also compromised (Gul & Ali, 2010).

One of the investigator strategies to eliminate participant-related barriers in terms of retention and recruitment is to ensure that the treatment conditions and data collection is convenient for the participant. They should take into account factors such as having flexible hours for participation, appropriate place to reach the patient, availability for the times that procedures will be conducted. Also, participants indicated that the time and place of the intervention is one of the highest motivation factors to join or not the study (Gul & Ali, 2010).

Regarding pregnant women, recruitment and retention is a big challenge. Pregnant women are a vulnerable group very underrepresented in clinical research. Understanding the barriers and challenges for retention of this population would help to advance in prevention and treatment options for them. Some factors found in the literature that influence retention of pregnant women in clinical research are: (Frew et al., 2014)

- Socioecological influences:
  - Research budget constraints
  - Prevalence of longitudinal studies requiring follow-up
- Social level factors:
  - Clinical accessibility
  - Strong relationship with research staff
  - Social network and family/partner influences
- Individual-level factors:
  - Voucher-based incentives
  - Time to complete the study
  - Pregnancy-health related issues
  - Demographic factors

It has been found that cash or gift incentives are associated with higher retention rates. In this way, budget planning in clinical trials should consider this kind of incentives when concerning pregnant women as participants. Also, women stated that time constraints, a need to return to work or transportation were common issues that affected their retention rates (Frew et al., 2014).

#### 4.2.2 Factors affecting patient participation in clinical trials

Patient recruitment is crucial for the success of a clinical study which explains the importance of identifying which factors affect to the decision-making process of a research participant to enroll or not in a clinical trial. A narrative review on factors affecting patient participation done in Ireland, found that the primary factor was related to personal gain such as receiving better or more treatment/care, access to novel treatments or obtaining more positive outcomes. However, other factors such as perception of risks, personal costs (time and financial), altruism, communication, physician influence, research process and demographics, were also involved. In this way, a good and trusting relationship with the physician was identified as a positive factor to participate and the physician ability to communicate the information in an appropriate manner has also impact on trial participation (Walsh & Sheridan, 2016).

Another study that measured the reasons given by patients for participating in phase I cancer trials, noted that the four main reasons for participation were: belief on a high expectation of medical benefit; the trial as the best available treatment option; to maintain hope; and to help future research. On the other hand, pressure from the family and friends was less important (Catt et al., 2011). However, it has to be taken into account that this type of patients is normally biased by their optimism.

#### 4.2.3 Factors affecting parental consent in paediatric clinical trials

Clinical research has been restricted in paediatric population for many years. However, nowadays the need to test drug safety and efficacy in this vulnerable population has been recognized, especially since results from adult studies cannot be extrapolated to children (Chappuy et al., 2006).

Regarding informed consent, paediatric research ethics requires that the best interests of the child are more important than the concept of autonomy (Chappuy et al., 2006). There is very little paediatric literature about the factors and reasons that affect parents' decisions to enroll their child in a clinical trial. In general, the available literature found that parents with a higher socio-economic status are less motivated to participate in clinical research because they tend to be less implicated in contributing with the medical knowledge. Also, a French study reported that parents' main reason to refuse to enroll their child in a clinical trial were safety concerns and unproven efficacy. A study conducted in the University of California, Davis, Sacramento, University of Washington, Seattle and Asthma Inc Research Center in Seattle, designed a questionnaire to identify the reasons and factors that influence parental consent.

This questionnaire was given to 44 parents whose children were participating in clinical research. From this study, the results obtained suggested that the most influential factor for giving consent is the opportunity for their child to learn more about his/her disease. This was followed by helping improve medical research scientific knowledge, and the benefit of receiving the newest drugs. Less motivated factors were the patient-research staff relationship, financial benefit, free medications and having free visits. And the less important factors were receiving gifts, location of the clinic, influence of family and friends, duration of study, type of treatment in the study and social support for being a research participant. However, it is important to note that children blood sampling procedures were minimized with a topical anaesthesia cream, which can explain why the type of treatment was not a relevant influential factor. (Rothmier, Lasley, & Shapiro, 2003) A study by Tait et al, remarks that the environment where consent is presented, is also an important factor that could influence in parental decision, suggesting that in an inpatient situation after a surgical procedure parents are more likely to consent (Tait, Voepel-Lewis, Siewert, & Malviya, 1998).

Another study evidenced that parents considered that understanding the risks and potential benefits for the child are the two most important factors to take into account when making a decision regarding their child's participation in a clinical trial (Chappuy et al., 2006; Tait et al., 2002).

Moreover, a study that interviewed 68 parents who enrolled their children in clinical oncology or HIV research, concluded that trust and quality of relationship with the investigator are the main values that parents seek before consenting, and that the majority of them preferred that the investigator take responsibility in the decision making process (Chappuy et al., 2006).

### 4.3 Re-consent

Informed consent is a continuous process of communication between investigator and participants where relevant and significant information such as new findings or useful test results, should be informed to research subjects, in case they change their decision to participate in the study. These updates can be done through newsletters that investigators usually send to subjects on the progress of research. (Resnik, 2009)

Biomedical research is increasingly relying on long-term studies where re-use of data and biological samples is often necessary, with the issue about under what circumstances a re-consent process is required or not. The aim of long-term studies is to ensure availability of samples and data for future purposes where new ideas, ways of research, uses, technologies, collaborations and possibilities can arise. This confronts with the traditional way of consent as a one-off event where the purposes and procedures are described in advance. (Dixon-Woods et al., 2017) Currently, longitudinal studies tend to use broad consent for future research purposes. However, sometimes broad consent is not enough and re-consent needs to be an option to allow subjects to make their own decisions.(Wallace et al., 2016)

Re-consent can be defined as the action where a research subject decides to participate again in a study or the decision to consent to new procedures, new elements and other updates of an existing study. It is the process of consent required to allow the use of data and samples for different purposes from which was originally given. However, it is important to distinguish between re-consent, where someone reconsiders the information to make the decision and re-affirmation, which is the re-expression of a decision that has been already made before. Re-affirmation is usually appropriate when a lot of time has passed between the first expression of willingness to participate in a study and the current situation, and it is usually fixed by sending a letter thanking the subjects for their participation and reminding their freedom to withdraw at any time. In the same way, resigning a document is not the same as re-consenting, because someone can sign a document without reconsidering their decision. (Dixon-Woods et al., 2017; Resnik, 2009)

The way of contact to re-consent can be in person, by phone, email or postal mail, where investigators explain the subjects the need for re-consent and give them enough time to ask questions. Signing a document may also be asked where subjects confirm their willingness to continue in the study. Moreover, in complex and high risk studies a new consent form is more appropriate to be asked to sign. (Resnik, 2009)

#### 4.3.1 Conditions under which re-consent is presented to participants

Different situations where a re-consent can be considered are (Dixon-Woods et al., 2017; Resnik, 2009):

- If the initial broad consent is not valid due to a very novel future use or because the new elements or uses of data are not under the terms and conditions proposed in the original broad consent.
- When an initial consent does not cover purposes for future research.
- Where there are significant modifications of the research protocol that are not in the original consent.
- When it is intended to revisit a group of subjects that belong to a study that has been latent for a while.
- When paediatric population reach adulthood, they need to sign the form again.
- When important risks related to the study have been failed to inform the participant.
- When the consent process was conducted in a time where the subject's capacity was compromised.
- When there is an inappropriate representative for a subject who is unable to consent.
- When the subject does not respond to treatment and its condition exacerbates.

Re-consent is also necessary when the original consent has been improperly signed or documented such as (Resnik, 2009):

- The participant forgot to sign the form.
- The legal representative that sign the form is not the adequate.

- The consent form is presented in a different language to the subject.
- The subject signs the wrong and outdated version.
- The study's approval had expired when the subject first signed.

#### 4.3.2 Re-consent psychological effects in participant's attitudes towards research

One of the potential problems of re-consenting is to trigger with patient emotional attitudes such as anger, stress and other perceptions such as violation of privacy or loss of trust, that may lead to possible subject's withdraws from the study, putting at risk the integrity of the study (Dixon-Woods et al., 2017).

Whereas re-consent is crucial for respecting the autonomy of a subject and protect their potential risks, it can also cause harm by producing anxiety and confusion against a situation where they can feel that their privacy is not being respected or when they have not given their permission to be re-contacted (Resnik, 2009).

Taking into account these emotional factors and that re-consenting may be costly to implement, it should only be presented when ethically required for protecting subjects rights and autonomy (Resnik, 2009).

Arguments in favour of re-consent state that it gives subjects greater autonomy and control over their data and samples, increasing thus, their trust on genomics research. There are some studies that have found that re-consenting enhances participants' feelings of control, trust and respect in the study, allowing them to make autonomous decisions and having the right to withdraw at any time (Wallace et al., 2016).

Arguments against re-consent emphasize on the process itself, which is costly and time consuming, and on the participants, causing stress and reducing the cohort size over time. All these, leads to difficulties to conduct research and compromises the scientific validity of the data. Moreover, "*consent fatigue*" is a term that refers to the loss of privacy that may cause distress for participants (Wallace et al., 2016).

Another aspect to consider is the situation where new genetic information is found. In this case, re-consenting seems to be necessary as it can have a potential impact on biological relatives and social families who have not consented directly and may not understand the implications on the study (Wallace et al., 2016).

Also, previous studies have shown that participants are more restrictive in hypothetical situations than in the real ones. For instance, some subjects in a study were totally surprised by the need for re-consent, feeling they already consented in the first time, whereas in hypothetical situations, results shown that participants and public prefer to re-consent for each new update of the study (Wallace et al., 2016).



In conclusion, there is a clear consensus between participants and public that re-consent can be oppressive, but in general, people still see the importance of being asked (Wallace et al., 2016).

### 4.3.3 Withdrawal due to re-consent

There are examples where subjects decide to withdraw from the study when they are asked to re-consent or re-sign a form. When this happens, study's recruitment goals and statistical power can be compromised and therefore, investigators often prevent to discuss these matters with subjects. Institutional Review Boards should be the organisms that decide whether the re-consent is necessary and provide the investigators with the appropriate guidelines and training to manage the procedure and overcome the possible conflict of interest (Resnik, 2009).

## 4.4 Therapeutic misconceptions and unrealistic optimism in clinical trials

Informed consent is a process designed for the protection of participants in clinical research (Lidz et al., 2004). The process entails the disclosure of relevant information such as the purpose of the study, procedures, benefits, and risks involved. It enables participants to autonomously make an informed and voluntary decision about whether or not to participate in the research study. There are various ethical issues involved with the informed consent process. Some of these derive from covert communication barriers and erroneous assumptions that can lead to false expectations. They can have direct implications for the psychological and emotional well-being of participants.

This section outlines the principal ethical concerns raised about the quality and validity of informed consent when the research participant's/patient's decision to participate in a clinical trial may be grounded on false beliefs or compromised by lack of understanding about the nature and purpose of the research. These concerns crystallise around the concepts of "*therapeutic misconception*" and "*unrealistic optimism*", which are discussed in more detail in this section.

### 4.4.1 The case of therapeutic misconception

The term "*therapeutic misconception*" was coined in the early 1980s by Appelbaum et al. (1982). They undertook a study, involving patients with psychiatric disorders, in which there was a documented failure of participants to appreciate the difference between clinical research (i.e. aiming to gather scientific data for generalisable knowledge) and medical treatment (i.e. aiming to improve individuals' health). This phenomenon was labelled "*therapeutic misconception*" (Appelbaum et al., 1982). Twenty-five years later, a consensus panel of experts suggested the following definition:

*"Therapeutic misconception exists if individuals do not understand that the defining purpose of clinical research is to produce generalisable knowledge,*

*regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial” (Henderson et al., 2007: 1736)*

According to Henderson et al. (2007), lack of understanding about the purpose of research is a common denominator for most definitions of therapeutic misconception that exist in the literature. However there are another two important points to consider in relation to this definition. First, it draws attention to the fact that the defining characteristic of research – as opposed to medical interventions – is its aim of creating generalisable knowledge. The researcher can, therefore discuss risks and benefits with the participant, but, unlike in a medical intervention, there are very limited alternatives to the trial (i.e. in most cases, the alternative to being in the trial is simply not being in it). Second, the definition does not link therapeutic misconception to over- or under-estimation of the benefits and risks of participation. The misconception is not of the benefits and risks of participation, but only of the purpose of clinical research.

Hornig and Grady (2003) provide a summary of the key features of therapeutic misconceptions in clinical research. These are:

1. The participant/patient believes that every aspect of the research project is designed to benefit the participant/patient directly.
2. There is a failure on the part of the participant/patient to understand that clinical research is distinct from medical treatment, in the applied methods and approaches followed.
3. There is expectation that in the research, personal care will be maximised and individualised as it is in routine clinical care.
4. There is a failure to understand research methodology and its implications – for example failure to understand the implications of randomisation and placebo controls; failure to understand risks of research-based procedures in the clinical trial.
5. The participant/patient believes that the researcher/physician has the participant’s/patient’s best health interests rather than the best interest of the research enterprise in mind.

Concerning points (1) and (2) mentioned above, there is a body of literature to indicate that most participants/patients misunderstand the purpose of Phase I in a clinical trial. They typically enrol for personal benefit, when in reality there is much uncertainty and only a low probability that they will experience any benefit at all during Phase I (Durand-Zaleski et al. 2008; Pentz et al., 2012). If participants/patients make the assumption that the central purpose of a specific clinical trial is therapeutic and that they will personally benefit from participation, then this false belief may motivate them to enrol for a clinical trial without having weighed properly the risks of participation in proportion to benefits.

The misconception alluded to at point (3) is picked up by the Declaration of Helsinki (WMA, 2013), which draws attention to the risk that research participants could mistake research

processes for routine care when research is combined with care (e.g. in teaching hospitals). Hospitals are thus identified as likely environments for therapeutic misconception on the part of patients/participants in research.

With regard to point (4) above, therapeutic misconception can also be the result of misinterpretations or misconceptions about specific clinical research-related concepts, including the meaning of terms such as *randomisation, placebo, benefits and risks* (Appelbaum et al., 2004). As discussed in Section 3.5, such medical terms are considered as particularly difficult to understand (Montalvo & Larson, 2014), and therefore culturally and linguistically diverse populations may be more vulnerable to therapeutic misconceptions.

As far as the last point (5) is concerned, this misconception is captured in Sugarman et al.'s (2005: 35) definition of therapeutic misconception as “[...] *the inaccurate belief on the part of participants in research that research procedures involve individualised treatments selected primarily for the benefit of the participants*”.

A study by Durand-Zaleski et al. (2008) documented the extent and identified predictors of therapeutic misconception in research. The study comprised two phases: the development of a questionnaire to assess the quality of informed consent; and a survey of patient subjects based on this questionnaire. According to the study results, therapeutic misconception was present in over two-thirds of respondents, who expected an individual benefit from participating in a clinical research study. The authors suggest that “*patients’ views on their participation was a mixture of self-interest and misconception with altruism and faith in medical progress through research*” (p. 4). Similar results were obtained by Pentz et al. (2012), whose study documented the frequency of therapeutic misconceptions and misestimation, and associations with therapeutic optimism, based on interviews and a survey with Phase I clinical trial participants. It was reported that therapeutic misconception was widespread for over two-thirds (68.4%) of the study sample, while therapeutic misestimation was nearly universal. The estimates of therapeutic misconception are uniformly high in participants in oncology Phase I clinical trials, while the misestimation of risk was the consequence of expressing an overestimation about the benefits.

This particular case with Phase I clinical trials is supported by the fact that as it constitutes the point of departure in a study, research participants often harbour a psychological need to be optimistic about the outcome. They subsequently tend to overestimate the probability of their directly benefitting from their participation, even if the researcher has explained otherwise. The question then is whether such an expressed therapeutic misconception can influence the researcher’s decision whether to enrol that person in the study. A valid point is made by Miller and Joffe (2013: 761), who state that “*although information disclosure is aimed at promoting research subject’s understanding and appreciation of the implications of study participation, there is no consensus about what subjects must understand or appreciate in order to give ethically valid consent*”. Within bioethics, autonomy is understood as having the opportunity to make voluntary decisions that reflect one’s own preferences and values.

Accordingly, what is important to assess for the validity of consent is whether it reflects a personal decision that is consistent with the participant's values and preferences. It does not follow that all kinds of misconceptions must necessarily undermine the capacity to give ethically valid consent.

Therapeutic misconception is manifested in different ways on the basis of a person's assumptions, expectations, beliefs and understanding of information presented and discussed with the researcher as part of the informed consent process. Every measure and effort should be made by the researchers to detect whether any therapeutic misconceptions exist for the person that enrolls for a clinical trial. Henderson et al. (2007), developed a type of assessment which identifies five dimensions of research that participants should understand to avoid therapeutic misconception. These are presented below:

- **Dimension 1** – Scientific purpose. Clinical research is designed to produce generalisable knowledge and to answer questions about the safety and efficacy of interventions under study in order to determine whether or not they may be useful for the care of future patients.
- **Dimension 2** – Study procedures. Participation in a trial may involve procedures or tests, in addition to the interventions under study, that are intended only or primarily to generate scientific knowledge and that are otherwise not necessary to patient care.
- **Dimension 3** – Uncertainty. For interventions under study in clinical research, there often is less knowledge and more uncertainty about the risks and benefits to a population of trial participants than there is when a doctor offers a patient standard interventions.
- **Dimension 4** – Adherence to protocol. Administration of the interventions under study is typically based on a strict protocol with defined dose, scheduling, and use or avoidance of concurrent medications, compared to administration of standard interventions.
- **Dimension 5** – Clinician as investigator. Clinicians who are in health care settings provide treatment; in a clinical trial setting, they are also investigating the safety and efficacy of an intervention.

#### 4.4.2 Unrealistic optimism and the implications for informed consent

While therapeutic misconception has been identified as a major ethical concern for clinical research over the last three decades, the scientific community also recognised the fact that the informed consent process is more complex than it might seem, i.e. that it is a process that extends beyond a simple act of information disclosure and exchange. As such, it cannot be assessed only on the basis of how well an individual/patient understands the information that is disclosed (Crites & Kodish, 2012): there is more to the participant's capacity to make a decision to take part than how well they understand the information. "*Unrealistic optimism*" is one very prominent example.

Unrealistic optimism has been defined by Jansen et al. (2011) as “*a bias that leads people to believe, with respect to a specific event or hazard, that they are more likely to experience positive outcomes and/or less likely to experience negative outcomes than similar others. The phenomenon has been seen in a range of health-related contexts—including when prospective participants are presented with the risks and benefits of participating in a clinical trial*” (p. 1). As explained by Jansen et al. (2011), in essence, unrealistic optimism affects how people process information. The problem is not so much that it prevents a person from understanding the benefits and risks generally associated with a course of action, but rather that it causes a person to misapply this information to herself.

In a study conducted in the context of early-phase oncology trials, it was found that unrealistic optimism may compromise informed consent (Jansen et al., 2011). The study included 72 patients with cancer who were enrolled in early-phase oncology trials. They were given questionnaires in order to evaluate indicators for unrealistic optimism, as well as participants’ understanding of the trials’ purpose. The results from this study indicated that almost two-thirds (60%) of participants exhibited unrealistic optimism in response to three of five questions about the likelihood of particular events happening to them compared with other trial participants: (1) *having their cancer controlled by drugs administered in the trials*; (2) *experiencing a health benefit from the drugs in the trials*; (3) *not experiencing a health problems from the drugs in the trials*. It was also found that any misunderstandings about the purpose of the study were not significantly related to the variable of unrealistic optimism, as the majority of respondents accurately understood that the purpose of the research was to advance scientific knowledge. Another study has indicated that unrealistic absolute optimism can be associated with feelings of disappointment and regret when outcomes fall short of expectations (Carroll et al., 2006).

Unrealistic optimism is sometimes though to admit a distinction between two forms (Shepperd et al., 2015). The first form is *unrealistic absolute optimism*, which refers to an unfounded belief that a personal outcome will be more favourable than the outcomes indicated by a quantitative objective standard. The second form is *unrealistic comparative optimism*, which refers to the erroneous estimate that one's personal outcomes will be more favourable than the outcomes of peers. Both unrealistic absolute optimism and unrealistic comparative optimism can have serious implications for decision-making and behaviour.

Jansen (2006) argues that unrealistic optimism can compromise informed consent in different ways than therapeutic misconception. Therapeutic misconception is closely associated with the “*understanding*” component of giving consent. Yet, as mentioned earlier in this section, unrealistic optimism is to some extent independent of understanding of the information provided about a study. Rather, unrealistic optimism interferes with *voluntariness*. Jansen (2006) distinguishes between two types of voluntariness: a *weak* conception of voluntariness, which places focus on external factors such as the absence of coercion or manipulation, and a *strong* conception of voluntariness, which requires in addition to the requirements of the

weak conception, a person free from various cognitive and affective distortions that interfere with autonomous decision-making.

Accordingly, unrealistic optimism would compromise informed consent at its core, if the strong conception of voluntariness is considered, since a person may consent to participate on the basis of an erroneous belief or distorted perception of risks. Jansen (2006) concludes that “[...] *potential research participants commit the therapeutic error only when they enrol in a trial that is not in their best medical interest. Reducing opportunities for participation in such trials would mitigate the problem of unrealistic optimism in clinical research*” (p. 18).

Unrealistic optimism and therapeutic misconceptions compromise informed consent at different levels. According to Lad and Dahl (2017), the “*expression of optimism*” occurs early in the process of consideration of participating in a clinical trial, and the same could be argued for some predispositions and misconceptions about clinical trials, or research in general. To raise the quality of informed consent, it is fundamental for researchers to consider and assess various factors that can contribute to optimistic bias, such as past experiences and perceived controllability.

## 4.5 Discussion

Psychological aspects towards informed consent are important factors to consider when approaching the informed consent process, especially with vulnerable populations. Scientific literature is consistent on the fact that investigator communication is crucial and thus, building a trust relationship between researcher/physician and participant/patient is very useful to engage subjects to participate in the study and contribute to positive levels of satisfaction while taking part in a trial. In fact, even the smallest gestures such as sending “*birthday*” and “*thank you*” cards are particularly valued by participants, as these help to develop positive emotions.

On the other side, re-consent is a process which can make participants experience a negative emotional state, such as psychological distress, feelings of mistrust, fatigue, etc. Therefore, it is important to establish whether it is appropriate or not to ask for re-consent from all subjects involved in a trial, taking into account their situation with respect to risk exposure, possibility to intervention and kind of information. It is ethically justifiable in clinical trials not to carry out processes that require time and effort for investigators, sponsors and patients when unnecessary.

In conclusion, asking or not for re-consent remains still as a challenge in clinical trials, and guidance on this process should be provided, in order to enhance patient recruitment, engagement, satisfaction and retention, always considering the impact of variables such as therapeutic misconceptions and unrealistic optimism, which affect at core how participants process and act upon the information made available.

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