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

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

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Table of Contents

Executive Summary

The present deliverable has been produced within the scope of Work Package 1 (WP1), *A multi-layered approach to informed consent*, which comprises Phase I of the i-CONSENT project. Specifically, this phase involves a comprehensive analysis of issues related to informed consent, as well as the identification of challenges and barriers toward an improved informed consent process in the frame of clinical research.

Deliverable D1.1 opens with a philosophical discussion about the notion of informed consent, which discusses the ethical basis for informed consent (Section 2). It continues to present the evolution of the conceptual framework built around informed consent as manifested in international guidelines and standards developed for obtaining informed consent in the context of clinical research. It determines which are the principal elements considered for presenting participants with adequate information, draws attention to specific provisions from selected guidelines that can lead to misconceptions about the process, and further identifies specific requirements presented for vulnerable populations with regard to the process (Section 3).

Finally, the deliverable provides a comprehensive narrative literature review of scientific studies to identify and analyse methods, techniques and strategies associated with improvement of informed consent in the context of clinical research. This review was not only limited to the identification of studies which focus on methods for improving readability of informed consent documents, but expanded to cover any aspects associated with the process itself to overcome barriers and challenges presented in the context of clinical research (Section 4).

To contextualise the later review and discussion, the deliverable begins with an overview of some of the most significant philosophical themes concerning the nature of consent. This begins with an account of the role of consent in the Western philosophical tradition. Following Johnston (2010), we recognise two streams: the role of consent as the legitimating basis of government and the state; and the role of consent in individual interactions and relationships. These streams slowly come together in the massively influential contributions of Kant and Mill, which are examined, and which can be seen as cementing the idea that the ethical importance of consent is grounded in its connection to the related concepts of autonomy, freedom of conscience, and freedom from outside interference.

The historical discussion yields two main insights. Firstly, the notion of autonomy has been subject to more than one interpretation. For example, Luther appealed to *freedom of conscience*; Kant drew on a technical sense of *autonomy* which is distinct from the sense typically used in contemporary bioethics; and Mill appealed to *individual sovereignty*. Secondly, the historical review shows that the normative force of consent has always required explanation in terms of other more basic concepts: consent is not in itself the kind of concept that can serve as a fundamental ethical basis or *justification*, and it has not generally been considered as such in the western tradition. Gathering informed consent is, then, in research

an ethical requirement, but the ethical justification must appeal to a concept or concepts beyond consent.

In order to consider what the ethical ground of consent might be, the deliverable examines informed consent's roots in the Nuremburg Code. From this we draw four important observations. Firstly, the ethical ground of consent is something *absolute* (not instrumental, not secondary, not derogable). Secondly, the ethical ground is *universal* (i.e. applies to all people, and is arguably grounded in or connected to universal rights). Thirdly, the ground is such that the responsibility of a researcher to gather consent is not a responsibility that can be delegated to another. Fourthly, the personal nature of this responsibility reflects the bi-directional, interpersonal character of the consent process: the goal is not a unilateral affirmation of consent by a research subject, but a transaction between two moral agents, the researcher and research subject.

Since the Nuremburg Code speaks of "voluntary consent", we go on to discuss the connection between consent and voluntariness. This leads us to challenge the view, presented by Maclean (2013) and Kleinig (2010), that there is a core moral notion of consent, and that this notion is such that voluntariness is a necessary condition of the legitimising normative force that is essential to it. We propose an alternative "thin" conception of consent, according to which it is not a core moral notion, and does not necessarily have a legitimising normative force in any strongly ethical sense (though it always has *some* normative force). This view has a number of advantages. Firstly, the view does no violence to the everyday notion of consent as a form of permission or licencing. Secondly, and more substantially, endorsing a thin conception of consent leaves open the possibility that consent processes have merely instrumental value, which stems from their being an effective means of securing a core ethical goal. That core ethical goal will likely be the ethical basis of consent.

We go on to examine the nature of *consenting* (the action/interaction). This gives rise to an explanation of the variety of background and framework norms that govern these kinds of interactions between these kinds of parties. In particular, we note the importance of norms of communication, which speakers are expected to respect and which have obvious implications for communication between the parties to the consent transaction. Communication between a researcher and research subject is context-dependent, norm-dependent, and goes beyond what is literally said in different ways. Accordingly, based on the philosophical background, we conceive of consent processes as having instrumental value stemming from their being an effective means of securing a core ethical goal. That core ethical goal has largely been taken to be *respect for the autonomy of the potential research subject*. However, autonomy is not the only ethical concept that could be proposed as the ethical justification for informed consent. Plausible alternatives include *protection of research subjects against deception, coercion, and other wrongs, or fairness or non-maleficence*. There is nothing to rule out informed consent being a protection of a number of rights and interests of potential research subjects, including the right to autonomy as well as to fair treatment, and a number of others.

The ICH E6 Guideline for Good Clinical Practice provides the following definition for informed consent (1.28): "*A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form*". A rather comprehensive definition about the concept of informed consent, which is further enriched by considering the following statement by the WHO Research Ethics Review Committee (ERC): "[…] *obtaining genuine informed consent from research participants is best thought of as a process of sharing information and addressing questions and concerns, rather than simply obtaining a signature on a prescribed form*".

Expanding a bit further on this, a genuine informed consent requires not only the full and complete disclosure of information, but also to ensure participants' understanding of the information provided at different phases of the study. Yet, this is not always the case. Depending on the characteristics of each study, the informed consent form and supporting materials can be lengthy and complicated, or have information presented in a format which offers limited understanding of technical terms (Grady, 2015). Over the past few decades, a substantial body of scientific research has concentrated on methods and interventions for improving participants' understanding the informed consent process in clinical studies. These interventions have mostly focused on modifying content, improving the format of informed consent documents (e.g. avoid using terms such as "therapy" or "treatment" which may misleadingly imply some benefit for participants in research), or introducing educational programs to enhance communication between clinicians and patients (Flory and Emanuel, 2004; Hoffner et al, 2012).

Evidence from systematic reviews seems to support a patient-centred approach, based on open and transparent communication, as studies suggest that extended discussions with researchers or clinicians is an effective way to improve participants' understanding (Flory and Emanuel, 2004; Nishimura et al, 2013), while the impact of using multimedia or other technological solutions in the process have shown mixed results (Campbell et al, 2004; Hoffner et al, 2012). In general terms, the improvement of informed consent as a process requires a combination of written, verbal, and multimedia formats, as well as the employment of various interviewing methods, such as the teach-back and teach-to-goal methods, as well as the cognitive interviewing technique. The most promising avenue for improving informed consent would be to consider this as a continuous and dynamic process, which needs to be tailored and consistent with research participants' values, interests and preferences during all phases of the research study.

Table of main results

Number	Short Description	Reference Page
1	The process of gathering consent is designed to ensure that certain ethical requirements concerning the relationship between the researcher and the subject are met. Gathering consent is, in this sense, an ethical requirement, but the ethical *justification* must appeal to a concept or concepts beyond consent.	Sec. 2.1 p. 12
2	There are advantages to endorsing a very thin conception of consent – i.e. one that does not insist upon its being "a core moral notion", nor upon its necessarily having a legitimising normative force in any strongly ethical sense (though *qua* permission or licencing it must always have *some* normative force).	Sec. 2.2.5 p. 23
3	The consenting relation is inherently communicative. Because the consent transaction is a type of communicative *action*, and because it involves a variety of speech acts, it takes place against an already present normative backdrop.	Sec. 2.3.1 p. 25
4	More recent readability assessments at international level, reveal that informed consent documents remain excessively lengthy and complex to read, while certain core elements are often omitted. There are various interventions that can be implemented for the improvement of informed consent documents, based on content, length, features, and structure.	Sec. 4.4 p. 54
5	Empirical evidence to date (Flory & Emanuel; Nishimura et al, 2013) indicates that extended discussions and face-to-face interaction, may be more effective than approaches using multimedia, or enhanced forms for improving understanding.	Sec. 4.5.1 p. 63
6	A combination of written, verbal, and some multimedia formats is generally considered as more effective a method in adhering to guideline requirements while enhancing participant understanding.	Sec. 4.5.2 p. 64
7	The cognitive interviewing method can be used as a means to assess the understandability of consent materials based on bidirectional exchange which can help in identifying misconceptions and addressing concerns.	Sec. 4.6.2 p. 68
8	The use of teach-back and teach-to-goal methods has shown to be particularly effective for increasing comprehension levels in relation to consent materials and the process.	Sec. 4.6.3 p. 70
9	The Clinical Trials Transformation Initiative launched a project which sought to define the specific barriers to successful informed consent processes and propose solutions to optimise this process.	Sec. 5.2 p. 75
10	12 EU-funded projects have been identified as relevant to i-CONSENT. Most relevant projects with the goals of WP1 were: HLREADGR (FP6), ETHICAL RISK (FP7), CONTRACT (FP7), SIFORAGE (FP7), PATIENTPARTNER (FP7)	Annex I

1. Introduction

Informed consent is a core ethical and regulatory requirement and one of the most important benchmarks of ethical clinical research. Informed consent is a process which requires that participants voluntarily confirm their interest and commitment to participate in a clinical research study.

There are four core criteria which are vital for obtaining valid informed consent: (a) disclosure, (b) understanding, (c) capacity, (d) voluntariness (Beauchamp & Childress, 1994). Typically, the quality of informed consent depends on the type and amount of information disclosed, adequate capacity and understanding of information, and a voluntary decision to participate in a clinical research study.

While the disclosure of adequate information is of utmost importance to enable participants to make an informed decision about their participation in a research study, the crux of informed consent is not just about disclosure or understanding. Informed consent is a process, which should also provide adequate opportunity for reflection, to evaluate participants' capacity to understand and act upon information, and to ensure that the decision to participate is completely voluntary.

In the past few decades, there have been considerable efforts to enhance transparency and openness in clinical research, particularly after the release of the ICH E6 Good Clinical Practice (GCP) Guideline in 1996, and subsequent amendments of the Declaration of Helsinki and the CIOMS Guidelines. Unfortunately, in the attempt to improve transparency by disclosing more information to research participants, informed consent documents and other related materials have become increasingly lengthy and complex over recent years (Albala et al., 2010; Berger et al., 2009).

Of course, a genuinely informed decision cannot be solely based on the volume of information presented, but also depends upon the extent to which any such information is understandable and retainable. While efforts to evaluate consent documents and materials have most commonly focused on the presence of specific elements, this is insufficient as it concerns only a part of a process, which is not static but continuous.

This report delves into the nature of consent from a philosophical perspective (Section 2), examines the international guidelines and standards which have shaped the concept of informed consent (Section 3), and identifies and summarises various approaches to improving the informed consent process based on evidence from the scientific literature (Section 4).

2. Philosophical aspects of informed consent

2.1 Consent in the Western tradition

Analysis of the nature of *consent* stretches far back in Western thought (to say nothing of other intellectual traditions[3]). This history may be thought of as comprising two distinct, though plainly related, streams (Johnston 2010). In social and political thought, the role of consent as the legitimating basis of government and the state has been contested throughout the tradition. Plato (1992[380BC]) was perhaps the most influential voice contesting consent's role, while the likes of Hobbes (1953[1651]), Locke (1993[1690]), and Rousseau (1987[1762]) set out positions in which political consent was – albeit in quite different ways – central (Johnston 2010: 26-34).

The second stream examines the role of consent in individual interactions and relationships. In this domain, Plato is again sceptical of the role of consent, arguing that individuals ought to live their lives, and find their place in community life, through focus on the tasks or roles for which they are best equipped: "What matters [for Plato] is that individuals be directed to the tasks to which they are best suited, a direction that can be best accomplished by those few members of society who possess wisdom" (Johnston 2010: 39-40). The Platonic view came under immediate intellectual pressure from, for example, his near-contemporary Aristotle, and was pressured in a tangible sense by the rise of Rome as the preeminent Western power. Rome – despite its origins[4], and certainly imperfectly[5] – was a society largely structured around a social, legal, and economic system based on individuals freely consenting to given transactions (Johnston 2010: 40-42). As Rome declined, so too the role of individual consent declined throughout societies of the Dark and Middle Ages. But the intellectual tradition survived and eventually revived. As Johnstone (2010: 44-45) notes, Christianity, in both the Catholic and Protestant traditions, played a role. The impact of Luther in particular is noteworthy, as it highlights the connection of consent with conscience, a relationship that is at the heart of our discussion in this document:

> Luther's thinking led to the notion that nothing can be more important to a person than freedom of conscience and, by extension, the freedom to shape his or her own life in accordance with his or her beliefs. […] [His] insistence on the importance of individual conscience was taken up by innumerable disciples and spread throughout Europe, signalling an enormous shift in values and priorities and heralding an era in which social relations were transformed by a newly acquired sense of the importance, and indeed, the sanctity of individual consent. (Johnston 2010: 44)

[3] Cultural variations in approaches to consent are discussed in deliverables D1.4/D1.7

[4] To mention only one of the most obvious examples, the abduction of the Sabine women in the early history of Rome does not indicate an all-encompassing insistence on the role of consent.

[5] Large numbers of people were not, or not fully, entitled to give their consent to the transactions by which they were bound (for example slaves, women, plebeians, and others).

It is important to notice that the concept with which this passage opens (*freedom of conscience*) is not the same as that with which it closes (*individual consent*). As our discussion progresses, we will begin to see connections between consent and other concepts, including conscience, autonomy, freedom, and fairness. Our goal is to attempt to understand the nature of these connections.

For now, however, let us draw from the passage quoted above the observation that consent is lauded not (or at least *not simply*) in its own right, but on account of its connection to another concept, freedom of conscience, which is "more important to a person" than anything else (at least on this view). Thus Johnston's interpretation of Luther seems to amount to this: that, in some sense at least, the importance of individual consent is explained by consent's connection to freedom of conscience. More specifically, the suggestion here is that individual consent is important because when social relations are grounded in the consent of the individual parties, those relations may be said to respect (or at least not undermine) the freedom of conscience of the individual parties.

The idea that the ethical importance of consent is grounded in its connection to the concept of freedom of conscience gathered further intellectual momentum and mass through its reinterpretation in the works of Kant (e.g. 1997[1785]) and, later, John Stuart Mill (2006[1859]).

Kant inevitably looms large in discussions of consent. His influence is, however, difficult to fully assess. This is because while Kant emphasised the importance of *autonomy* to moral philosophy, the way in which he understood and deployed that concept is somewhat idiosyncratic and, in any case, arguably differs markedly from its use in (non-Kantian) discussions in contemporary bioethics. This document is not the place for prolonged discussion of Kantian ethics, but fortunately Manson & O'Neill illuminate the above point concisely:

> Those who [in writing on bioethics, medical and research ethics] invoke Kant's legacy and authority almost invariably overlook the fact that Kant used the term *autonomy* to refer not to a characteristic of individuals, but to the formal properties of principles of action that can serve for all, and in particular to the combination of law-like form and universal scope. […] In speaking of "autonomy of the will", Kant refers to a property of the practical principle an agent adopts or "wills". He, of course, thinks that agents can choose freely – but their doing to does not make their willing autonomous: heteronomous – that is non-autonomous – action is also free and imputable. (Manson & O'Neill 2007: 17-18)

Despite such difficulties, Kantian conclusions – if not the details of the arguments by which he arrived at them – can be brought to bear in discussions of informed consent in more direct ways. Kant's categorical imperative, in its first formulation, states that one should "act only in accordance with that maxim through which you can at the same time will that it become a

universal law" (1997[1785]: 31/G4:421[6]). The imperative is "categorical" in that it applies to all rational agents independently of any particular goals they may have. Rationality, for Kant, presupposes freedom of the will and this in turn entails (through the Kantian account of the *autonomous* will – i.e. the will that is a "law to itself (independently of any property of the objects of volition)" (1997[1785]: 47/G4:440)) that a rational being should act only on those maxims that can be willed as universal laws (i.e. categorical imperatives). (Note that this does not imply that rational beings act always in conformity with the categorical imperative, but merely states that "anyone who has humanity [i.e. is a rational being] has a capacity and disposition to follow such principles; but since his rationality may be imperfect or counteracted by other features, he may not always follow these principles" (Hill 1980: 86).) This rational nature, this aspect of humanity (of what it is to be a person), is held by Kant as an end in itself. That is to say, this rational nature is to be valued for its intrinsic nature, rather than in virtue of some extraneous factor (for example, instrumental value of some kind or other). Since, Kant argues, we each value our own rational nature as an end in itself, and since we recognise that all other rational beings value their own rational natures on the same grounds as we value ours, we must therefore value their rational natures as we value our own (1997[1785]: 38/G4:428-9). Thus, we arrive at the humanity formulation of the categorical imperative: "Act in such a way that you treat humanity, whether in your own person or in any other person, always at the same time as an end, never merely as a means" (1997[1785]: 38/G4:428-9).

In the humanity formulation of the categorical imperative we see a clear ethical ground for informed consent: the informed consent process provides a way of mitigating the risk that research subjects be treated as means to scientific ends, rather than as ends in themselves. We will discuss the possible ethical grounds of informed consent in more detail below. Here however we would like to draw to the attention of the reader the following consideration. If we accept the point summarised above by Manson & O'Neill (2007: 17-18), then the Kantian claims just made turn not so much on autonomy – whether autonomy is understood in the technical Kantian sense or any other – as on some other ethical concept, such as dignity or fairness (depending on how we interpret the idea of treating persons as ends in themselves). But we will pick up this thread later on.

Mill (2006[1859]: 16) famously stated that: "Over himself, over his own body and mind, the individual is sovereign". Contrary to certain claims, it should probably not be said that the appeal to sovereignty "overlaps substantially with Kant's principle of humanity" (e.g. Miller 2010: 380) – or at least it should not be said without precise argument and textual analysis in support (cf. Manson & O'Neill 2007: 17-18). Nonetheless, while acknowledging Manson & O'Neill's point regarding the dangers attached to any simple translation of the Kantian notion of autonomy into other contexts, we might still note that the categorial imperative, in the formula of humanity, appeals to the intrinsic nature of persons, and to the role of autonomy

[6] The page number (31 in this case) is provided, as well as a reference to the pagination given in the standard German edition of Kant's works (G4:421 in this case).

therein; and we may, therefore, proceed to an examination of the relation between autonomy and consent, independently of the Kantian account of autonomy. Here, as Miller (2010: 380) puts it, "The legitimacy of the way that competent adults treat each other depends on it being consistent with their autonomy (literally, self-rule)."

Autonomy as self-rule, is typically associated, in this context, with Mill's *harm principle*. This principle insists that intervention to obstruct a person in pursuit of some freely undertaken action, is justified only to the extent that the action is likely to harm another person:

> The only purpose for which power can be rightfully exercised over any member of a civilised community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant. He cannot rightfully be compelled to do or forbear because it will be better for him to do so, because it will make him happier, because, in the opinions of others, to do so would be wise, or even right. These are good reasons for remonstrating with him, or reasoning with him, or persuading him, or entreating him, but not for compelling him, or visiting him with any evil in case he do otherwise. To justify that, the conduct from which it is desired to deter him must be calculated to produce evil to someone else. Over himself, over his own body and mind, the individual is sovereign. (Mill 2006[1859]: 16)[7]

We should like to elicit two points – to be developed further as our discussion progresses – from the very brief review of the historical development of the role of consent in Western thought presented in this section.

As Johnston clearly demonstrates, a trajectory certainly can be traced from the origins of the Western intellectual and ethical traditions (including religious, scriptural sources, which Johnston discussed but we have not) through to our own times:

> Mill's harm principle can rightly be regarded as the apotheosis of the idea that all entitlements and obligations should stem from the wills of individuals as expressed by their freely given consent. […] The publication of *On Liberty* in 1859 represents the high water mark of a movement […] that led western thought from […] a low regard for the value of social relations based on individual consent to a vision of a society in which virtually all such relations would stem from the wills of individuals through consensual agreements. […] Indeed a century and a half after Mill's work appeared, we remain within a long historical moment in which, in western societies, the notion that individuals should be subject only to those obligations to which they have freely given their consent retains enormous power, power that continues to be apparent in the resolutions of innumerable legal and social issues. (Johnston 2010: 49)

This trajectory situates individual autonomy at the centre of the discussion of consent. However, it should be noted – and this is the first point we wish to elicit – that, as we have

[7] And this passage finishes with the sovereignty claim mentioned previously: "Over himself, over his own body and mind, the individual is sovereign" (Mill 2006[1859]: 16).

seen, the notion of autonomy has been subject to more than one interpretation. Even in our very brief and skirting discussion, we have covered major figures appealing to notions which, while certainly related, are not identical (at least not on the face of it): Luther appealed to *freedom of conscience*; Kant drew on a technical sense of *autonomy* which, as Manson & O'Neill noted, is distinct from the sense of autonomy at play in contemporary bioethics (and we should not assumed there is only one sense at play in contemporary bioethics); and Mill appealed to individual sovereignty. Thus if – as the mainstream view has it – the ethical basis of consent is autonomy, there remains much to be said of autonomy.

Secondly, we wish to highlight a structural point about the discussion of consent, namely that throughout the tradition, and throughout our discussion, consent itself has always required justification. That is to say, the issues of the ethical basis of consent has always been at issue. For example, consent might be cited as the justification (ethical basis) of the operation of political power; but consent itself is then supported (justified, given an ethical basis) by some other concept (such as autonomy, the harm principle, or whatever). The point, then, is simply that consent is not in itself the kind of concept that can serve as a fundamental ethical basis or justification, and it has not generally been considered as such in the western tradition.

Summarising, and drawing our two points together, though consent is sought and provided in many different situations, it is not sought *tout court*, but as a means of ensuring that some other ethical justification is satisfactorily met. That ethical justification may be respect for autonomy – however that concept is finally understood – but it may be something else. In ensuring that interventions in the lives of others – in our case: the inclusion of a research subject in a study – are legitimate, the gathering of consent serves a practical purpose: the process of gathering consent is designed to ensure that certain ethical requirements concerning the relationship between the researcher and the subject are met. Gathering consent is, in this sense, an ethical requirement, but the ethical *justification* must appeal to a concept or concepts beyond consent.

This important point will be further supported in the following section, with reference to the appeal to voluntariness in the Nuremberg Code. For now, let us note two important conclusions. In order to improve the informed consent process, we need to understand:

1. which concepts (beyond consent) are appealed to as the justificatory ethical basis of consent;
2. how specific steps in the informed consent process can be added, changed, or removed to make a better and more reliable connection between the process and the achievement of its aims, namely to ensure that the fundamental ethical requirements of the researcher-subject relationship are satisfied.

The first of these points is addressed in Section 2.3. The second is addressed in Section 4.6.

2.2 Ethical foundations of consent in the Nuremberg Code

In this section we examine a key source of the requirement on researchers to ensure that research subjects give consent to their participation in a study: The *Nuremberg Code* of 1947.

Our intention is not to provide a historical account, nor to provide a comprehensive conceptual analysis, but rather to explore the justificatory ethical basis of the requirement for consent as found in what is arguably the foundational source on research ethics.

2.2.1 The Nuremberg Code: Principle no. 1

The Nuremberg Code was developed during the "Doctors' Trial", held in Nuremberg, Germany, 1946-7, at which Nazi physicians of the Third Reich were accused of murder and torture in conducting experiments on inmates of concentration camps. Seven of the 23 defendants received the death sentence, five life imprisonment, four imprisonment for between 10 and 25 years, and seven were acquitted (Shuster 1997).

The Nuremberg Code sets out ten principles defining the rights of participants in medical research. Of these, we focus only on the first (the others are briefly addressed later on in this document:

> 1. The voluntary consent of the human subject is absolutely essential.
>
> This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.
>
> The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

This statement raises many questions concerning, for instance, its scope, the intended interpretation of certain phrases, as well as details of how it might be practically implemented. These issues are addressed elsewhere in subsequent sections of this document. Here we focus on the ethical foundations to which the statement appeals.

2.2.2 Exploring the ethical ground of the Nuremberg Code

An absolute ground

Let us firstly note that the statement does not include (and was not intended to include) any *direct* reference to its ethical ground. However, since voluntary consent is said to be "absolutely essential", we may infer that the consent requirement is based on a ground that is absolute. To be absolute, an ethical ground must be unshakeable in the face of any other factor. It should thus emanate ethical force in and of itself, by virtue of its own nature: it may not instrumental; it may not be secondary to a more fundamental ground; it may not be derogable.

A universal ground

Secondly, in its appeal to "voluntary consent of *the human subject*", the definite description denotes a class rather than an individual (just as "the lion is a mammal" refers to all lions, not any individual lion). Accordingly the claim is universal: all humans, regardless of any other factor or fact about them, must give voluntary consent to their individual participation. This is a startlingly strong requirement, bearing in mind that many cases in which genuine consent is either *not possible* (e.g. minors, unconscious patients) or is *difficult to assess* (e.g. when full mental capacity is questionable, or when the force of an earlier consent later seems questionable) are routinely recognised. Yet the statement continues with, what is in effect, an underlining of this requirement – that "the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, …" and so on – with no reference to any possibility of legitimate participation in its absence (e.g. through a parent consenting on behalf of a minor). The full strength of this requirement may not have been intended by the judges who drafted the Nuremberg Code. It seems reasonable to conclude, however, that they had in mind that the Code be grounded on *universal* rights and expectations. The ethical ground of the statement is thus something universal.

No delegation of duty or responsibility

Thirdly, it is worth noting the final paragraph of the statement, which says that the "duty and responsibility for ascertaining the quality of the consent […] is a personal duty and responsibility which may not be delegated to another with impunity". Note firstly that this strongly implies that what is at stake is a genuinely moral duty and responsibility, rather than, say, a (merely) legal or professional requirement (though of course it may be these as well). To say that the duty is "personal" is to forestall any defence or excuse for misconduct stemming from lack of consent which amounts to "but I delegated this responsibility". While the practical responsibility for ensuring proper consent may, as a matter of fact, be delegated, the moral responsibility cannot – as a matter of conceptual necessity – be so delegated.

The transactional character of the consent process

Fourthly, the personal nature of the responsibility for ascertaining the quality of the consent sheds further light on the ethical foundations of the entire statement. It shows that the

process through which voluntary consent is established is genuinely bi-directional and interpersonal. What is at stake is not a unilateral affirmation of consent by a research subject, but rather a transaction between moral agents (researcher and research subject). (On this see section 2.3.1 below)

2.2.3 Autonomy or non-maleficence?

Given all that has been stated so far, it is natural to read the Nuremberg Code as grounding the requirement for voluntary consent in *autonomy*, understood as the ability "to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion". But as pointed out by Tom Beauchamp, this is not the only interpretation. He writes:

> In the 1940s, the Nuremberg Code presented a forceful insistence on voluntary consent in research but had not distinguished clearly between appeals to autonomy and appeals to on-maleficence ("do no harm") as the justificatory basis of consent requirements. (Beauchamp 2010: 58-9)

This is an important point, and should remind us that while the Nuremberg Code does speak of research subjects exercising "free power of choice", it does so in *explanation* of *what* is meant by the insistence that voluntary consent is "absolutely essential" – it does not do so as a *justification* of *why* voluntary consent is essential. Moreover, as pointed out by Manson & O'Neill (2010: 2-4), the Code itself makes no explicit mention of autonomy. Indeed Manson & O'Neill (2010: 16-7) go further than Beauchamp, implying that the Nuremberg Code is not simply unclear as to whether the justificatory basis of consent requirements is autonomy or non-maleficence but comes down on the side of non-maleficence:

> The Nuremberg Code was rather clear about the reasons for thinking that consent justifies. It views informed consent as assurance and evidence that a proposed action will not involve or be based on force, fraud, deceit, duress, constraint or coercion, and the like, and so will neither force the body nor overwhelm or undermine the will. Consent matters because it can be used to protect research subjects and patients against grave wrongs. (Manson & O'Neill 2010: 16-7)

However here it is again worth reminding ourselves that when the Nuremberg Code speaks of preventing "the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion" from undermining the research subject's free power of choice, it does so in explanation of the *meaning* of the claim that voluntary consent is "absolutely essential", not in ethical justification of that claim.

2.2.4 Voluntariness and consent

It is extremely important here to distinguish two senses in which voluntariness may be at stake. In the first place, there is a logico-semantic question as to whether the idea of involuntary consent is coherent. Secondly, there is an ethico-philosophical question as to whether involuntary consent – if such a thing is possible – is capable of delivering the ethical

or normative force that is required to make consent morally transformative. Let us begin with the logico-semantic question.

As a matter of linguistic meaning in English, "consent" connotes not simply agreement, but permission. Thus while to *assent* to something (usually to a statement) is to agree with it, to *consent* to something (usually a proposed action or plan) is to give permission that it may occur or continue to occur.[8] Is it possible, then, to involuntarily give permission? *Prima facie*, it would seem so. Two kinds of case are readily imagined: "accidental consent", when a person unintentionally signals consent and thereby gives permission; and "unwilling consent", when permission is granted intentionally, but unwillingly. Let us review both.

Accidental and unwilling consent

Accidental consent may be dismissed as not really consent at all. On condition that the signalling of consent was not reckless, it would be unjust to hold a person to commitments to which they had unintentionally signalled consent, even if the "signal" was given voluntarily (i.e. if the person did not realise that their action would be taken as a signal of consent). If a person raises their hand to scratch their nose and that gesture is taken by an auctioneer as a bid on an artwork, it would be unfair to hold them bound to buy the piece.[9] Or consider a related case in which legislators have acted on this form of intuition. European directive 2002/58/EC ("the ePrivacy Directive") provides that visitors to any website be informed of and agree to the use of cookies on that site before they take effect.[10] This, in effect, outlaws any appeal on the part of website operators to implicit consent. Now implicit consent is not the same as accidental consent, but the logic is similar: visiting a website shall not be taken as a signal of consent to the use of cookies, unless it is clearly indicated to the user, and they agree, that their continued use of the site presupposes or constitutes consent to the use of cookies. The ePrivacy Directive thus protects website visitors against inadvertently signalling cookie consent by forcing the consent process into the open. (In the same way, an auction house could, if it chose, take special steps to ensure that visitors fully understand what gestures may be taken by auctioneers to constitute bids.) Accidental consent, we conclude, is not a form of involuntary consent. What then of unwilling consent?

Cases in which the signal of consent is apparently provided against the will of the person so-consenting will tend to be susceptible to explanations that remove the appearance of involuntariness. Typically, the appearance of involuntariness arises because the consenting person can be said to have consented to something to which they would not have consented in the absence of other factors. Though it is important to remember that what is at stake here is the voluntary quality of the decision to consent – not any positive feelings towards the course of action consented to. Unsurprisingly, the "other factors" are crucial. The fact that

[8] The terms "assent" and "consent" obviously have technical meanings in the context of research and healthcare. However to draw on these as terms of art would, at this stage of our discussion, beg the question.
[9] The example is adapted from Miller & Wertheimer (2010a: 85).
[10] *Directive on privacy and electronic communications 2002*. In fact the ruling is a little more complicated, with some cookies exempt. For a brief summary see European Commission (2016).

you would not, in the absence of a serious risk to your life, consent to an invasive medical treatment with long-term negative side-effects, does not render your consent involuntary. In such a case you are faced with a dilemma and must select, voluntarily, the least bad option. The fact that you would not, in the absence of a violent criminal holding a gun to your head, consent to their request that you hand over your money, does not render your consent to the transaction involuntary. Certainly your consent in no way absolves the attacker of wrongdoing, but that is another matter. Arguably the consent is void or invalid; but its invalidity stems from your assailant's having illegitimately put you in position in which all the options are bad. Our position is therefore that involuntary consent – taken as consent provided against the will of the consenter – is not possible: apparent cases of involuntary consent are, in reality, either cases of voluntary consent in which the consenter harbours negative feelings towards to the course of action consented to; or cases in which the (supposed) signal of consent was in fact misconstrued.

This view is not accepted across the board and, as we shall see, there are situations that seriously challenge the view. However, in briefly examining the alternative view, which we oppose, we will shed further light on the ethical basis of consent.

Alasdair Maclean summarises two approaches to accounting for the relationship between consent and voluntariness. On the first view, involuntary consent is possible, but lacks normative force.

> First, voluntariness could be seen simply as essential to the normative force of consent. This would mean that an involuntary consent would still be consent but it would not have the power to legitimise the intervention. (Maclean 2013: 139)

The second view holds that voluntariness is essential to consent and, therefore, that an act that lacks voluntariness cannot be an act of consenting.

> If consent is to act as a permission that alters the legitimacy of an act then it must be wilfully and freely given. Without the freedom to give or withhold it, consent loses its moral (and legal) force and is reduced to being a normatively meaningless assent that lacks the power to legitimise the act. […] The second strategy would be to argue that a lack of voluntariness means that the given permission is not, in fact, consent. (Maclean 2013: 139)

This second view is similar to our own insofar as it holds that involuntary consent is not possible. However the view does not deny that a *permission* is given in "involuntary consent" cases, it only denies that this permission constitutes consent.

Maclean holds that the first and second views are, on some level, equivalent. This is plausible: the first view holds that involuntary consent is consent without legitimising normative force; the second view holds that involuntary consent is a variety of permission which, since it lacks voluntariness, lacks legitimising normative force. Therefore, the choice between them is an aesthetic or practical one. Maclean endorses the second on grounds of "simplicity and

clarity", though acknowledging that this takes us away from the everyday sense of "consent" and toward a decidedly technical sense (2013: 139).

A similar approach to Maclean's is taken by John Kleinig (2010)

> [O]ne might do what would ordinarily be taken to signify consent without actually consenting. This occurs when a person is coerced into agreeing to something. We may more appropriately speak of this person as assenting than as consenting. Because consent transforms the moral relations that exist between persons, the signification must be voluntary. Assent that is given under duress does not have the moral force of consent. (Kleinig 2010: 12)

Like Maclean, Kleinig views consent – at least in the sense that occupies us in discussions of informed consent for research activities – as inherently morally transformative. He makes the limited subject of his attention explicit as follows:

> What I am concerned with articulating here is not everything that might be graced with the label of "consent" but with a core moral notion […]. Although consent figures quite importantly in certain formalised contexts—especially the law—it draws its strength in those contexts from the sense that I have characterised as morally transformative. (Kleinig 2010: 4).

This claim – that there is a core moral notion of consent, and that this notion is such that voluntariness is a necessary condition of the legitimising normative force that is essential to it – is at the heart of Kleinig's account of the Valdez-Wilson case (Westen 2013; "Rapist who agreed to use condom gets 40 years", 1993). This is a case which, if we are to support our view, requires careful explanation.

The Valdez-Wilson Case

Kleinig writes of the Valdez-Wilson case as follows:

> When Joel Valdez broke into Elizabeth Wilson's apartment and sought to rape her at knife point, she agreed to submit if he wore a condom. He had sex with her for an hour until she was able to flee to a neighbour's apartment. But a Texas grand jury decided that her agreement to have sex if he wore a condom constituted consent to intercourse and therefore that she was not sexually assaulted. Given that Wilson negotiated her agreement under the threat of serious injury, her assent did not possess the moral force of consent. Coerced responses need not be strategically bereft, and evidence of physical resistance is no prerequisite of refusal to consent. (Kleinig 2010: 12)

So on Kleinig's account, Wilson assented but did not consent; or to put it in Maclean's terms, insofar as Wilson granted a form of permission, it was not consent.

The grand jury decision is horrific.[11] Setting aside legal definitions, the "correct" interpretation of the Valdez-Wilson case – from the point of view of ethics; from the point of view of common sense – is that Wilson was sexually assaulted, was raped, was fundamentally wronged. The Kleinig/Maclean view secures this interpretation by denying that Wilson consented to intercourse. If we are talking about the decision of the grand jury, bound, as they presumably were, by legal definitions, then it clearly matters a great deal whether or not the intercourse was correctly considered consensual.[12] However, we are not here focussed specifically on the correctness of the legal decision the grand jury arrived at. (Note that it is impossible to be sure why the grand jury returned the verdict it did. The grand jurors deliberated in secret and made no explanation of their decision (Westen 2013: 1-2).) Rather we are focussed on the ethical basis of the wrong that Elizabeth Wilson suffered. On our view, the grand jury verdict is horrific not (or not only) because the grand jurors judged that she had consented to intercourse, but rather because they ended up (presumably by a legal argument) at the absurd conclusion that she had not been sexually assaulted. Leaving aside legal definitions and requirements, it is possible to simultaneously hold the views that Wilson consented to intercourse with a condom *and* that she was raped. It follows from this that consent, even when voluntary, is not a sufficient condition for legitimising the course of action consented to.

There is certainly something slightly unpleasant about claiming that Wilson consented to intercourse with Valdez, so let us be clear about what exactly we are claiming. As far as consent to intercourse goes, we are making only a very limited claim, namely that Wilson, in an extreme and very unfortunate set of circumstances, granted a form of permission to Valdez. In effect, she gave consent to one of a range of horrendous options. Valdez wronged, raped, and sexually assaulted Wilson because he put her in the position in which she was limited to that terrible range of options. The fact that Wilson consented to one of those options rather than any other (or none) is irrelevant to the question of whether she was raped.

The point made above could be summarised as follows. The second paragraph of the first clause of the Nuremberg Code is merely an explanation of *what is meant by* the first paragraph and, as such, cannot in any straightforward way serve as evidence for an account of the justificatory, ethical basis of consent requirements. That being so, let us focus further attention on the first paragraph. In particular, let us ask: why does it speak of "voluntary" consent?

[11] It was later overturned ("Rapist who agreed to use condom gets 40 years", 1993).

[12] If the options facing the grand jurors were: (a) decide that Wilson did consent, and thus conclude, as a matter of legal definition, that no rape occurred; or (b) decide that Wilson did not consent, and thus that she was raped; then they would – if they endorsed our account of voluntariness and consent – face an ethical dilemma: stick to your conceptual guns and deliver an unjust (even if strictly legal) verdict; or ignore your conceptual position on voluntariness and consent and deliver the right, the just, verdict.

2.2.5 A "thin" conception of consent

What is the significance of our dispute with the Kleinig/Maclean account of the Valdez-Wilson case? And how does this relate back to the appeal to voluntariness in the first clause of the Nuremberg Code (especially in light of our denial of the possibility of involuntary consent)?

We devoted an extended discussion to the Valdez-Wilson case because it demonstrates, relatively clearly, that the Kleinig/Maclean view – namely, that there is a core moral notion of consent, and that this notion is such that voluntariness is a necessary condition of the legitimising normative force that is essential to it – is, at the very least, not compulsory. That is to say, there is an alternative view, which has a number of advantages. The first advantage is that our alternative view does no violence to the everyday notion of consent as a form of permission or licencing. The second and more substantial advantage is that by endorsing a very thin conception of consent – i.e. one that does not insist upon its being "a core moral notion," nor upon its necessarily having a legitimising normative force in any strongly ethical sense (though *qua* permission or licencing it must always have *some* normative force) – we leave open the possibility that consent processes have merely instrumental value, which stems from their being an effective means of securing a core ethical goal. That core ethical goal will likely be the ethical basis of consent. Thus what Kleinig, following Hurd (1996), calls consent's "moral magic" – i.e. that which makes it morally transformative – is not intrinsic to it, but is derivative upon whatever serves as its ethical justification. That justification may, as on Maclean's view, be *autonomy*[13], or it may be something else.

The significance of this for our interpretation of the Nuremberg Code's explicit appeal to "voluntary" consent may be set out as follows. Our discussion has yielded two significant points: firstly, that "involuntary consent" – taken as consent provided against the will of the consenter – is not possible; secondly, consent, while always exerting *some* normative force, does not, in and of itself, exert a strongly ethical, legitimising normative force (we offer a "thin" conception of consent which does not insist upon its being "a core moral notion"). From the first point, we might suggest that the appeal to voluntariness is unlikely to be best-interpreted as an injunction against reliance on involuntary consent. A more plausible interpretation is that consent ought to be voluntary in the sense that the subject, by consenting, licences a course of action that they *genuinely, positively endorse*. This means that ideally the subject is not forced to select the best of a set of bad options (unlike in the case where a patient consents to life-saving invasive medical treatment with long-term negative side-effects), and in any case that he or she has the option of not participating at all (unlike in the Valdez-Wilson case). The use of the concept of voluntariness to emphasise the subject's genuine, positive endorsement of the course of action consented to, makes perfect sense if, as per the second point, we are operating with a thin conception of consent; whereas the "core moral notion" conception of consent endorsed by Kleinig and Maclean

[13] E.g. "Autonomy is concerned with the idea of moral agency: that we should be free to make our own decisions and to take responsibility for the ensuing consequences. Thus, if consent is to act as a permission that alters the legitimacy of an act then it must be wilfully and freely given" (Maclean 2013: 139).

would cast "consent" to courses of action that are not genuinely, positively endorsed as not really consent at all.

There is, if our view is correct, nothing in the nature of consent itself that works the transformative moral magic. That moral magic takes place at a deeper level, courtesy of the ethical concepts that form the true justificatory basis of the informed consent process. We would like to suggest that by drawing out the above interpretations of the appeal to voluntary consent in the Nuremberg Code, we have provided a strong, reasoned argument for engaging with whatever innovations in the informed consent process – even quite radical approaches – most effectively secure the goals of that process. What are those goals? In the broadest terms, they are to ensure that the core ethical concepts and requirements that motivate the consent process in the first place are duly satisfied. What are those core ethical concepts and requirements? What is the justificatory ethical basis of consent? This is question we address in the next section.

2.3 The nature of consent

We have seen above that the Nuremberg Code outlines a number of requirements on valid consent, including that the research subject should have the legal capacity to consent, should have sufficient understanding of what participation involves, and so on. These requirements – and the developments and additions contained in other resources since Nuremberg, are discussed below (see Section 3). In this section we focus instead on the nature of *consenting* itself. What exactly is going on when one person gives their consents to another in respect of some course of action?

2.3.1 The logical form of consent

Consent, as we have seen, is a form of permission. What is its logical form? We will take as our exemplar a simple and, by stipulation, uncontroversial case. Let's suppose that Alice (*A*) gives her consent to Bob (*B*) that he may record audio-visual footage of her morning routine in order to observe how she copes in daily life with some sort of medical implant (*p*). LF, we will say, is the basic logical form of the consent transaction.

(LF) *A* gives consent to *B* that *B* may *p*.

LF has three components:

1. the parties to the consent transaction, *A* and *B*;
2. the "gives consent to" relation; *and*:
3. *p*, the course of action that is licenced by the consent transaction.

We will examine each of these components in turn, starting with *A* and *B*, the parties to the consent transaction.

The parties to the consent transaction

Given that consenting is a normative act, the parties to the consent transaction must have an appropriate degree of normative agency. This raises two very large questions. What is an "appropriate degree" of normative agency? And what is normative agency anyway?

Taking the second question first, we obviously cannot give a full account of agency here, so let us speak in the broadest of terms before appealing to a more precise account which has been influential in the literature.

An *agent* is generally taken to be an entity with the capacity to perform intentional acts; *agency* is the capacity to so act (Schlosser 2015). By *normative agency*, we mean, in the broadest possible sense, the capacity to act and react, intentionally and with understanding, in response to normative demands. And by *normative demands* we mean, roughly, demands dictating that an agent ought to react in a certain way (Darwall 2001). To be a little more specific, we draw on the work of James Griffin.

Griffin has written extensively on normative agency and its connection with human rights. Human rights, on Griffin's view, are protections of normative agency, which he describes as having three "stages" or components. Quoting at length:

> Normative agency has stages. The first stage consists in our assessing options and thereby forming a conception of a worthwhile life, where […] the sort of "conception" I have in mind is not a map of the whole of a good life, which is of doubtful value, but characteristically piecemeal and incomplete ideas about what makes a life better or worse. That is what I have been calling "autonomy". To form and then to pursue that conception, we need various kinds of support: life itself of course, a certain level of health, certain physical and mental capacities, a certain amount of education, and so on. I have been calling these "minimum provision". And these are not enough for agency if others then stop us; we must also be free to pursue that conception. I have been calling this "liberty". All human rights will then come under one or other of these three overarching headings: autonomy, welfare, and liberty. (Griffin 2008: 149)

Griffin's account of normative agency provides both a sharper answer to our second question, and the beginnings of an answer to the first (concerning an "appropriate degree" of normative agency).

Normative agency *in general* requires autonomy, welfare, and liberty. More specifically, in order that *A* is genuinely able to give consent to *B* that *B* may *p*, *A* must satisfy certain conditions that are mandated by the particular context in which the consent is sought. In the cases of informed consent concerning us, conditions will include those set out in the various guidelines and standards for informed consent presented in Section 3 below. These typically include that *A* should be: of an appropriate age; conscious; mentally sound; free from coercion or other undue outside influence, including severe pain or distress; suitably well-informed, and so on. When these conditions are not met, inclusion of *A* in a study will

certainly be unjustified unless further conditions, detailing procedures for including research subjects who are unable to consent, are satisfied.[14]

A further interesting aspect, stemming from Griffin's account of normative agency, is the importance of "forming a conception of a worthwhile life". This brings into focus the temporal aspect of the consent transaction. Consent is requested and given at a certain time, but it normally binds the parties for a longer period. Consequently, when *A* gives consent, he or she is making a commitment that, other things being equal, they will consider themselves bound by their consent until such time as either the course of action to which they have consented is complete, or they take explicit steps to revoke the consent. It follows that the duration of the consent should be clearly stated and understood by both parties; that both parties should be aware of exactly when the course of action to which *A* has consented will be considered to have ended; and that a clear and simple mechanism is available by which *A* can signal to *B* that they revoke their consent. In cases where personal data or biological samples are taken from *A*, there should be clear processes by which *A* can ascertain that upon revoking consent, those data or samples will be destroyed or anonymised, or whatever the two parties initially agreed. Unsurprisingly, there are far fewer stipulations regarding *B*'s capacity to enter into the consent transaction. After all, it is natural to assume that, in all cases which concern us, *B*, as the person conducting the research, will be of an appropriate age, mentally sound and so forth. However, it is worth considering what kind of circumstances might undermine or limit a researcher's capacity to enter into a consent transaction.

Researchers seeking the consent of potential research subjects take upon themselves, in virtue of entering into consent transactions, responsibilities; and these responsibilities – insofar as they are ethical duties at least – fall upon them individually, as physicians or researchers, rather than on their superiors or on their institution. The Nuremberg Code, as we have seen, speaks of the "personal" duties and responsibilities of researchers, and insists that these duties and responsibilities "may not be delegated to another with impunity". There is, then, a possibility for researchers find themselves entering into consent transactions under various forms of pressure – for professional advancement, to satisfy senior researchers, and so on. It is not only research subjects who are at risk of coercion. Just as research subjects may find themselves in unequal power relations with researchers (especially when the researcher is also the subject's physician), so the researcher may be subject to unequal power relations, albeit relations that exist beyond the confines of the particular consent transaction at hand.

The "gives consent to" relation

The morally transformative character of the "gives consent to" relation is one of the most fascinating aspects of the consent transaction. It is no surprise that the issue has already arisen several times in our discussion to this point. Recall that, as we interpreted their

[14] The provision of conditions for the inclusion of research subjects who are not capable of consenting is one respect in which later guidelines – such as the Declaration of Helsinki (WMA 2013) – are far more highly developed than the Nuremberg Code.

positions, Kleinig (2010) and Maclean (2013) endorse a view according to which there is a core moral notion of consent, one for which, due to its intimate connection with the concept of autonomy, voluntariness is a necessary condition of its consent's legitimising normative force. Our view, on the other hand, evokes only a thin conception of consent. Consent's morally transformative character – its "moral magic" (Hurd 1996) – is, on our view, not intrinsic to it, but derivative upon the deeper ethical concepts, whatever they may be, that form its true justificatory basis.

What kind of relation is the "gives consent to" relation? Or to rephrase the question in a more practicable form: when one gives consent, what kind of action is that? There are three possibilities (Kleinig 2010: 9-10). Firstly, consent could be a kind of mental state. On this view, for it to be true that *A* consents, it would suffice that *A* undergo or experience a certain kind of affirmative mental state. Secondly, consent could be entirely performative in character.[15] That is to say, the fact of consenting is brought about by an agent's performance of an action (perhaps a very specific action, such as signing a consent form or uttering certain words at a certain time). On an extreme version of this view, for it to be true that *A* consents, it would suffice that *A* performs the appropriate action. Thirdly, consent could be constituted by some combination of an affirmative mental state and an expressive, communicative performance.

We endorse the third view which is, quite plainly, the view which is presupposed by standard norms of informed consent, as described by the various guidelines discussed in Section 3. Some kind of affirmative mental state is a necessary condition of consent. Absent the affirmative mental state, consent is either actively withheld (e.g. if there is a negative mental state), passively not given (e.g. if consent is never requested, and thus the relevant mental state, affirmative or negative, never arises), or not capable of being offered (e.g. if the potential research subject lacks the requisite cognitive capacity). But an affirmative mental state is not, on its own, a sufficient condition of consent. Given the grave responsibilities that fall on the researcher when consent is given, the inclusion of a performative element is necessary to give them the reassurance of being able to later on demonstrate – by producing evidence of the performance – that consent was given. Yet the performative element of the consent transaction is not a sufficient condition of consent, since the appropriate action can be performed accidentally (see Section 2.2.4 above).[16]

The consenting relation thus not only requires a certain kind of intentional mental state on the part of the consenting party, but also an outward signification to the other party (Kleinig 2010: 11-12). The consenting relation is inherently communicative. Now because the consent transaction is a type of communicative *action*, and because it involves a variety of speech acts

[15] On performatives the *locus classicus* is Austin (1962).

[16] If we individuate actions by reference to the intentions of the agents performing them, it could be argued that a supposed accidental performance of the given action is not in fact a performance of *that* action, but of a different action. We will not pursue the argument here. In the end, this line of argument casts the performative element of consenting as a sufficient condition, but at the cost of including the mental element in the definition of the relevant action to be performed. It is thus equivalent to our hybrid view.

(Green 2015), it takes place against an already present normative backdrop (Manson & O'Neill 2007: 26-7).

> Communication is a normative affair that presupposes a rich framework of *shared* norms, and shared background commitments (practical and cognitive), as well as the requisite *inferential* competences. […] There is a wide variety of norms, ethical and epistemic, that are important for successful communicative actions. (Manson & O'Neill 2007: 65)

Notice how well this fits with our account of the connection between voluntariness and consent in Section 2.2.5. As the quotation above makes plain, there is in fact variety of ways in which a consent transaction can fail: any of a number of ethical or epistemic norms can be violated – voluntariness is not the only ethical norm at play.[17] Turning now to successful consent transactions (those in which the "moral magic" works), we need not appeal to a single "core moral notion of consent" (as per Kleinig (2010) or Maclean (2013)), but can appeal instead (or *as well*) to the wide range of shared norms and commitments that underwrite the possibility of this kind of communication.

In general, communication is governed by norms that speakers are expected to respect (even though the vast majority of speakers never explicitly realise that such norms are operative). The first systematic exposition of such norms, with respect to general conversation, was provided by the philosopher Paul Grice. The norms – he calls them *maxims* – he proposed are summarised in the figure below.

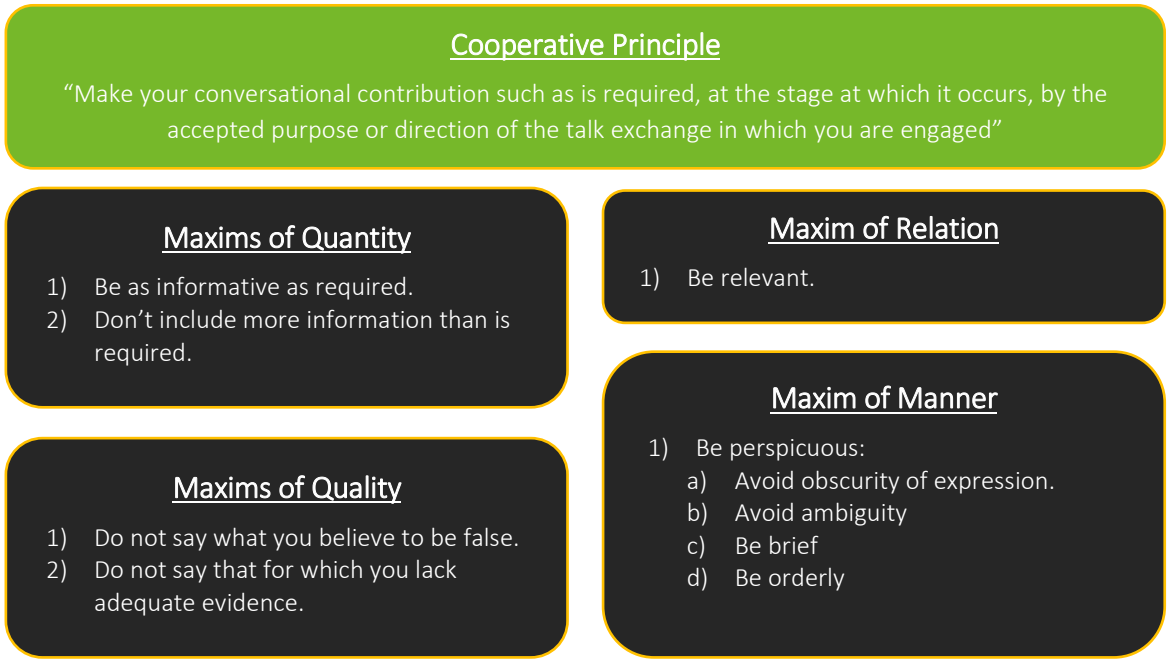

Fig. 1 - Gricean maxims of conversation.

Content adapted from Grice (1989: 26-7)

[17] This is part of the reason why our approach is able to provide a convincing account of the Valdez-Wilson case (see Section 2.2.4 above)

Although these maxims were not developed with consent transactions in mind, the applicability is obvious. Manson & O'Neill (2007) – who are explicitly discussing informed consent – clearly have Grice in mind when they discuss the standards for communication (2007: 68-96). They write, for example:

> Successful communication must in the first place use a language that its audiences can follow, and make what is said *intelligible* to them. It must also be *relevant* to its audience, rather than overwhelming them with a flood of irrelevant or distracting – even if intelligible – information. Would-be communication that flouts or disregards these norms fails because it is not adequately adjusted to its audiences. (Manson & O'Neill 2007: 85)

There is indeed a great value in conceptualising the consent transaction as an inherently communicative action. Reflection on the communicative, ethical, epistemic, and other norms associated with "giving consent to" yields a number of advantages, summarised by Manson & O'Neill (2007: 95, list format added).

- The justification of medical and research practice need not place sole or excessive weight on appeals to individual autonomy.
- A consideration of the normative underpinnings of consent shows why medical and research practice that provides public goods cannot be subject to informed consent requirements.[18]
- By thinking of informed consent as waiving important norms, it becomes clear that it can never provide a complete justification of any medical treatment or research proposal, since it presupposes other ethical, legal or professional standards, norms and rules.
- If informed consent transactions are seen as waiving those standards, norms and rules in limited ways, a robust distinction can be drawn between genuine and bogus ways of requesting and giving consent.
- It affords a relatively clear view – although not a uniform or simple view – of the standards that those who give and refuse consent must meet.
- These standards avoid reliance on excessive and questionable conceptions of explicit or specific consent.

The course of action that is licenced by the consent transaction

The fact that *A* gives consent to *B* does not give *B* permission to do whatever they like, but only some particular (course of) action. In terms of components, this is captured in LF by the inclusion of *p*, which is an explicit statement of what it is that, if *A* consents, she licences *B* to do. In terms of structure, this is captured through what, in the philosophy of language and philosophical logic, is known as a "that-clause".

[18] The point here is that some research, e.g. at the public health level, does not directly concern individuals but rather communities. In such fields individual autonomy, while not necessarily irrelevant, cannot be the only relevant justificatory ethical concept or principle. See Manson & O'Neill (2007: 18-19) and O'Neill (2004).

That-clauses are clauses, usually sentential in form, that follow the word "that" in propositional attitude reports (and similar linguistic contexts). A propositional attitude is a cognitive stance that an agent may take towards a proposition (for example believing *that today is Tuesday*, or doubting *that Arsenal will win the match*. A "proposition" is variously understood to be either a linguistic entity, i.e. a declarative sentence (a sentence in the indicative mood), or whatever is meant by such sentences, i.e. what one believes when one believes what is meant by a declarative sentence (which is a controversial metaphysical issue that we will ignore).[19] That-clauses are important for a variety of reasons. For our purposes, the main point to be aware of is that that-clauses typically introduce *opaque contexts*.

An opaque context is a linguistic form in which co-referring terms cannot always be substituted *salva veritate* (i.e. the substitution is prone to alter the truth-value of the original sentence). To illustrate, consider first some simple arguments, (A) and (B), whose validity is guaranteed by the fact that, in these contexts, co-referring terms *are* substitutable *salva veritate*.

(A1) Cicero is a famous Roman orator.
(A2) Cicero is (identical to) Tully. *Therefore:*
(A3) Tully is a famous Roman orator.

(B1) Pelé is the greatest Brazilian footballer.
(B2) Pelé is (identical to) Edson Arantes do Nascimento. *Therefore:*
(B3) Edson Arantes do Nascimento is the greatest Brazilian footballer.

When we introduce propositional attitudes – and hence opaque contexts – arguments of this simple form start to break down. Consider arguments (C) and (D), which are (at least on one plausible account) *invalid*.

(C1) Lois Lane believes that Superman can fly.
(C2) Superman is (identical to) Clark Kent. *Therefore:*
(C3) Lois Lane believes that Clark Kent can fly.

(D1) Simon knows that 64 is larger than 63.
(D2) 64 is (identical to) 2^6. *Therefore:*
(D3) Simon knows that 2^6 is larger than 63.

The conclusions of arguments (C) and (D) are false: if you were to ask Lois if she believes that Clark Kent can fly, she would deny it; and Simon, let us suppose, has no idea what 2^6 amounts to and thus can hardly be said to know that it is larger than 63.[20]

[19] For an overview of propositions and propositional attitudes see McKay & Nelson (2014) or any reliable introduction to the philosophy of language, e.g. Morris (2007).
[20] There is a massive literature discussing such cases. It cannot simply be assumed without argument that (C3) is false (after all, there is *some* sense in which Lois could be said to believe, of the man who is Clark Kent (i.e. Superman), that he can fly. And we could say something similar of (D3). But this takes us well off-topic here. For present purposes, all that matters is that the persons concerned (Lois and Simon) are disposed to deny that they

In opaque contexts then, it really matters *how* the that-clause is phrased. And thus in consent transactions – whose logical form, recall, is "*A* gives consent to *B* that *B* may *p*" – it really matters how *p* is phrased (see also Manson & O'Neill 2007: 12-16). Suppose that *q* is equivalent to *p*. Given the opacity of the that-clause in LF, it cannot be assumed that that *A*'s having consented to *B* that *B* may *p* will entail *A*'s having consented to *B* that *B* may *q*. And yet, given the equivalence of *p* and *q*, when *B* performs *p*, he or she will, as a matter of logic, perform *q*. An example reported by Faden & Beauchamp (1986: 183) and later adapted by Manson & O'Neill (2007: 13) illustrates the problem. Suppose that *A* consents to being given lysergic acid diethylamide as part of a study. It is not at all difficult to imagine that someone who doesn't know that lysergic acid diethylamide *is* LSD would be more willing to be given the former than the latter.

It follows that researchers should take care to ensure that potential research subjects are aware of any relevant:

- propositions or actions which are equivalent to the propositions or actions to which they have been asked to consent;
- propositions or actions which are entailed by, or which are logical or practical consequences of, the propositions or actions to which they have been asked to consent.

Determining which equivalent or entailed propositions or actions count as "relevant" may not be simple. This problem of establishing what is relevant and what not, it very serious, since there is no guarantee that what is irrelevant to one potential research subject is not relevant to another.

The problem of opaque contexts is only one of a variety of difficult issues attending the requirement to appropriately inform potential research subjects. Manson & O'Neill (2007: 34-8) suggest that there is a tendency to downplay or ignore the normativity of communication (which we discussed above) by miscasting it as relatively simple process of transferring discrete information between people, like passing a ball from person to person. From their discussion, in conjunction with the various points raised above, and also the conversational maxims of Grice, we wish to highlight the following important points about the process of communicating information to potential research subjects.

1. *"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.
2. *"Informing is norm-dependent"* (Manson & O'Neill 2007: 41-2; also Grice 1989: 28-9). Communication depends on background ethical, epistemic, and conversational

believe/know the respective claims. This suffices to support the points we wish to make about informed consent transactions.

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.

3. *What is communicated often goes beyond what is literally said: it matters how you say something* (Manson & O'Neill 2007: 44; Grice 1989: 22-143) 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.
4. *What is communicated often goes beyond what is literally said: "informing is inferentially fertile"* (Manson & O'Neill 2007: 46-7; also Grice 1989: 22-143). An audience can typically make a large number of inferences from what a speaker says. The speaker can anticipate some of these; indeed he or she may intentional attempt to elicit some of these. Other inferences cannot be predicted because they depend on the audience's background knowledge or beliefs.

All these points, as well as others discussed above, are relevant when we consider how best to approach the challenge of developing the most effective ways of communicating effectively with potential research subjects.

2.3.2 Consent as a practical means to a moral end: but what end?

We have argued for a thin conception of consent, that is, a conception that does not insist upon consent being, in a strong sense, "a core moral notion," nor upon its necessarily having a legitimising normative force in any strongly ethical sense (though of course we do not deny that consent must always have *some* normative force). It follows on our view then that a person can consent to some course of action and yet still be wronged by that course of action.

In the context of informed consent in research, we conceive of consent processes as having instrumental value stemming from their being an effective means of securing a core ethical goal. That core ethical goal has largely been taken to be *respect for the autonomy of the potential research subject*. We have seen above how this autonomy-based analysis can be seen as developing out of philosophy and the history of ideas in the Western tradition, out of ready interpretations of the Nuremberg code, and out of plausible approaches to issues concerning the nature of consent.

It is worth noting that autonomy is not the only ethical concept that could be proposed as the ethical justification for informed consent. Moreover, it has been subject to severe criticism on a number of occasions by Onora O'Neill (e.g. O'Neill 2002; 2003; Manson & O'Neill 2007). What other concepts could be appealed to? O'Neill herself has argued that informed consent is primarily valuable as a guard for potential research subjects against deception, coercion, and other wrongs. One might invoke concepts such as *fairness* or *non-maleficence* to capture these intuitions. In the end though, there is, in the absence of any argument to the contrary, nothing to rule out informed consent being a protection a number of rights and interests of

potential research subjects, including the right to autonomy, to fair treatment, and a number of others. This observation chimes with the account of normative agency proposed by Griffin (2008: 149). Recall that for Griffin, normative agency includes autonomy, welfare (minimum provision), and liberty; and these three concepts are what human rights protect.

In the end, it is not necessary to provide any firm conclusion here. What is important is that we reflect on the nature of the informed consent process, the way in which it relates to its justificatory ethical bases (whatever these may ultimately be), and the way in which it is affected by the framework of ethical, epistemic, social and other norms that is always present in communication. Informed consent processes are a practical means to a moral end. The task now – in i-CONSENT generally and, more narrowly, in the remainder of this document – is to begin to investigate what innovations can be made to improve the informed consent process so that it better achieves its moral ends.

3. International guidelines and standards for informed consent

Informed consent is a central tenet for the ethical conduct of research, which embodies the need to protect participants' autonomy and well-being, and to ensure that research is aligned with their own values, interests and preferences (Emanuel, Wendler & Grady, 2000). Informed consent is viewed as valid in clinical trials if a participant understands the following: study purpose, study protocol, risks, benefits to self, benefit to others, freedom to withdraw, alternatives, duration of study, voluntariness, confidentiality, and whom to contact (Tait et al., 2005). In the communication discipline, informed consent has been characterized as "*a complex exchange of information between professionals and patients that occurs through both interpersonal and mediated communication*," where the process is only meaningful "*to the extent that communication is complete, transparent, and effective*" (Donovan-Kicken et al., 2012).

A broad definition of informed consent in the context of clinical research is that of "*a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form*" (ICH E6 Guideline for Good Clinical Practice, 1.28).[21] This definition underlines two core criteria associated with informed consent, as provided by Beauchamp and Childress (1994), namely (a) *voluntary decision* and (b) *disclosure of all relevant information*, in addition to the (c) *capacity to understand the relevant information*, and (d) *comprehension of information*.

In the attempt to provide a more accurate definition of what constitutes *genuine* informed consent, the WHO Research Ethics Review Committee (ERC) does take into consideration those criteria, specifying that "*obtaining genuine informed consent from research participants is best thought of as a process of* ***sharing information and addressing questions and concerns****, rather than simply obtaining a signature on a prescribed form*".[22] This consideration is critical for understanding the conceptual evolution of the process of obtaining informed consent. The consent process includes several core elements which require information to be shared by the research team with the prospective participant in a manner that can be adequately grasped and acted upon.

Bhutta (2004) presents a conceptual framework for the elements and determinants of the process of developing informed consent, which comprises three main steps. First, the researcher provides full and transparent information about the research study and participant rights, in a clear and coherent manner. Second, the participant must understand what is being asked from him or her. This is a critical step, and can only occur if the information is

[21] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Guideline for Good Clinical Practice (E6)R1 (1996). Available from <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf>

[22] WHO Research Ethics Review Committee (REC). *The process of obtaining informed consent*. Available from: <www.who.int/rpc/research_ethics/Process_seeking_IF_printing.pdf>

presented in a manner that is simple yet conveys the key elements of the research study. Third, the participant must freely agree to take part in the research. This suggests that not only must the participant understand the research study, but s/he must also be competent to provide his/her consent.

Over a course of 70 years, several types of guidelines have been developed by international organisations, with the aim to establish an operational framework for the ethical conduct of research, specifying key principles, requirements and standards related to process of obtaining informed consent from participants (see Table 1).

This section collects and summarises the requirements and standards associated with obtaining informed consent as presented in international guidelines for clinical research. Any specific provisions made for vulnerable populations[23] are also reported in this section. This analysis shall provide an opportunity to identify similarities and controversies in relation to several aspects of informed consent, and further provide the basis for deepening the discussion about methods and approaches for improving informed consent in clinical research.

Table 1: List of international guidelines on the ethics of biomedical research with participants.

GUIDELINE	SOURCE	YEAR
Nuremberg Code	Nuremberg Military Tribunal decision in United States v Brandt	1947
Declaration of Helsinki	World Medical Association (WMA)	1964, 1975, 1983, 1989, 1996, 2000, 2008, 2013
Belmont Report	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	1979
International Ethical Guidelines for Biomedical Research Involving Human Subjects	Council for International Organizations of Medical Sciences (CIOMS) in collaboration with World Health Organization (WHO)	1982, 1993, 2002, 2016
Good Clinical Practice: Consolidated Guidance (ICH GCP E6)	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	1996

3.1 The Nuremberg Code

The Medical Case (Doctors) Trial in Nuremberg (1946) exposed to public view the unethical medical practices and inhumane experiments performed by Nazi scientists during the Second World War. Developed as part of a judicial decision condemning these acts, the Nuremberg Code (1947) is a 10-point statement meant to establish a core framework for the ethical

[23] Vulnerable populations are defined by the Council for International Organizations of Medical Sciences (CIOMS) as "*those who are relatively, or absolutely, incapable of protecting their own interests*".

conduct of research, in order to prevent future abuse of human participants. It states that, above all, participation in research must be *voluntary*.

The Nuremberg Code has not been officially adopted in its entirety as law by any nation or as ethics by any major medical association. Nonetheless, its influence on global human-rights law and medical ethics has been profound (Shuster, 1997).

The 10 points of the Nuremberg Code are as follows:

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Despite the heightened awareness of the need for safeguards and guidelines for human experimentation, it remains debatable whether the Code had a significant impact on the actual conduct of medical research and clinical practice.

According to Bhutta (2004), it was not until the Declaration of Helsinki in 1964, and the subsequent development of the CIOMS Guidelines, when the scientific community came closest to consensus-driven international guidelines for the ethical conduct of research.

3.2 The Declaration of Helsinki

In 1964, the World Medical Association (WMA) approved the *Ethical Principles for Medical Research Involving Human Subjects* (also known as the Declaration of Helsinki of the 18th WMA General Assembly), as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data (WMA, 2013).

Originally developed as a remedy for perceived lacunae in the Nuremberg Code (Ezekiel, Wendler & Grady, 2000), the Declaration of Helsinki has been revised several times ever since – most recently at the Fortaleza, Brazil WMA General Assembly (64th, October 2013).

The current version includes 37 principles laid out in 12 different sections, which are representative of various facets of clinical research (Table 2).

Table 2: List of sections comprising the Declaration of Helsinki (WMA, 2013)

Section	Article(s)
Preamble	1,2
General principles	3,4,5,6,7,8,9,10,11,12,13,14,15
Risks, burdens and benefits	16,17,18
Vulnerable groups and individuals	19,20
Scientific requirements and research protocols	21,22
Research Ethics Committees	23
Privacy and confidentiality	24
Informed consent	25,26,27,28,29,30,31,32
Use of placebo	33
Post-trial provisions	34
Research registration and publication and dissemination of results	35,36
Unproven interventions in clinical research	37

Informed consent

The Declaration of Helsinki includes a section dedicated to informed consent. It is evident that the principle of voluntarism established in the Nuremberg Code is reinforced in the Declaration of Helsinki, where it is stated that "*Participation by individuals capable of giving informed consent as subjects in medical research* ***must be voluntary***" (Article 25).

The document further specifies that potential participants must be "***adequately informed*** *of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the* ***right to refuse to participate*** *in the study or to* ***withdraw consent*** *to participate at any time without reprisal*." (Article 26).

Of interest, there is another statement in the same paragraph which reads: "*Special attention should be given to the* ***specific information needs*** *of individual potential subjects as well as to the* ***methods used to deliver the information***." (Article 26). This explicit requirement is an important addition to this section, as it is recognised that understanding of information may vary according to personal characteristics and may be influenced on the basis of different contextual factors.

Vulnerable groups

Requirements about the protection of vulnerable groups and individuals in the context of clinical research appear as a separate section in the document. It is specified 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***." (Article 19). Also, it is stated that "*Medical research with a vulnerable group is* ***only justified if the research is responsive to the health needs or priorities of this group*** *and the research cannot be carried out in a non-vulnerable group. In addition, this* ***group should stand to benefit from the knowledge, practices or interventions*** *that result from the research*." (Article 20).

While there is no specific provision about any safeguards or procedures that need to be in place, either to protect vulnerable individuals from particular risks or evaluate their capacity to understand all information presented, this gap is partially filled by Article 26 as presented above.

3.3 The Belmont Report

The Belmont Report[24] was issued in 1979 by the US Commission for the Protection of Human Services of Biomedical and Behavioral Research, entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. It is considered as one of the most significant works in the field of ethics and health research (Sims, 2010). The report sets forth three fundamental principles underlying the ethical conduct of research:

[24] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. (1979). Available from <http://ohsr.od.nih.gov/guidelines/belmont.html>

- **Respect for persons.** Incorporates at least two fundamental ethical considerations, namely (i) respect for autonomy, and (ii) protection of persons with impaired or diminished autonomy.
- **Beneficence.** Refers to the ethical obligation to maximise benefits and to minimise risks.
- **Justice**. Refers to the fair distribution of the benefits and burdens of research.

The report explains how these principles apply in the context of research studies, on the basis of three principal requirements: (i) Informed consent, (ii) Assessment of risk/benefit ratio, and (iii) Appropriate selection of research participants. For the purposes of our analysis, we shall focus on the requirement specific to informed consent.

Informed Consent

The Belmont report outlines that the informed consent process comprises three major elements: ***information***, ***comprehension*** and ***voluntariness***. The report does not only set out principles in relation to these elements, but provides valuable points to consider within the scope of this analysis.

As stated in the report, while guidelines for research establish specific items for disclosure intended to assure that participants are given sufficient information (see Article 25 in the Declaration of Helsinki), "*a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided*." (p. 11). To overcome this limitation, the ***reasonable volunteer*** is proposed as a standard: "[…] *the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge."* (p. 11). The report makes it clear that the means and context by which information is conveyed to participants may be considered as important as the information itself.

Another key point in the report is relevant to the element of voluntariness. It is specified in the report that in order to take a decision to participate in research, it does not only require conditions free of coercion, but also undue influence. The definitions provided for these conditions are as follows: "***Coercion*** *occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance.* ***Undue influence****, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance*." (p. 14).

Vulnerable groups

Similarly to the Declaration of Helsinki, the Belmont report also makes reference to the risks associated with the involvement of vulnerable groups in research. Seen under the prism of risk/benefit ratio and the need for systematic assessment of risks and benefits in the process, it is stated that "*when vulnerable populations are involved in research,* ***the appropriateness of involving them should itself be demonstrated****. A number of variables go into such judgments,*

including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. ***Relevant risks and benefits must be thoroughly arrayed*** *in documents and procedures used in the informed consent process*." (p. 17).

3.4 CIOMS Guidelines

In 1982, the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) created and released the *International Ethical Guidelines for Health-Related Research Involving Human Subjects*, also known as the CIOMS Guidelines. The 4th version of the CIOMS Guidelines (2016) considers that several developments had taken place since the previous version in 2002, including heightened emphasis on the importance of translational research, a felt need to clarify what counts as fair research in low-resource settings, more emphasis on community engagement in research, the awareness that exclusion of potentially vulnerable groups in many cases has resulted in a poor evidence base, and the increase of big data research.

The scope of the 4th version is broadened from biomedical research to cover other health-related research, which involves health-related data for instance. In the Preamble of the Guidelines (p.12) it is suggested that the term "health-related research" is used to refer to activities designed to develop or contribute to generalisable health knowledge within the more classic realm of research with humans, such as observational research, clinical trials, biobanking and epidemiological studies. Generalisable health knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based related to health, which can be corroborated by accepted scientific methods of observation and inference.

Informed consent

Guideline 9 is entitled "Individuals capable of giving informed consent". It determines that "*Researchers have a duty to provide potential research participants with the information and the opportunity to give their free and informed consent to participate in research, or to decline to do so, unless a research ethics committee has approved a waiver or modification of informed consent*". It further makes explicit that informed consent should be understood as a process, and participants have a right to withdraw at any point in the study without retribution. According to Guideline 9, researchers have a duty to:

- seek and obtain consent, but only after providing relevant information about the research and ascertaining that the potential participant has adequate understanding of the material facts;
- refrain from unjustified deception or withholding of relevant information, undue influence, or coercion;
- ensure that the potential participant has been given sufficient opportunity and time to consider whether to participate; and

- as a general rule, obtain from each potential participant a signed form as evidence of informed consent. Researchers must justify any exceptions to this general rule and seek the approval of the research ethics committee.

On the commentary of this Guideline, it is specified that "*Information must be provided in **plain language** understandable by the potential participant. The person obtaining informed consent must be knowledgeable about the research and capable of answering any questions from potential participants. Researchers in charge of the study must **make themselves available to answer questions at the request of participants**. Participants should be offered the opportunity to ask questions and receive answers **before or during the research**. Researchers should make every effort to address those questions in a **timely and comprehensive manner***" (p. 34).

With regard to the process, informed consent is described as "*a **two-way communicative process** that begins when initial contact is made with a potential participant and ends when consent is provided and documented, but **can be revisited later** during the conduct of the study. Each individual must be given as much time as needed to reach a decision, **including time for consultation with family members or others***" (p. 34). These are particularly important points with regard to the process and efforts toward a robust framework to support the decision-making process in the context of clinical research.

Moreover, some recommendations are provided by the Guidelines with reference to the content and features of the informed consent materials provided to prospective participants to improve understanding. Specifically, it is suggested that "*All potential participants should be provided with a written information leaflet that they **may take with them**. Informing the individual participant must not be simply a ritual recitation of the contents of a written document. The wording of the leaflet and any recruitment material **must be in language understandable by the potential participant** and be approved by the research ethics committee. The wording of the leaflet must be **short and preferably not exceed two or three pages**. An oral presentation of information or the **use of appropriate audiovisual aids**, including pictographs and summary tables, are important to supplement written information documents to aid understanding*" (p. 34).

Another key element is *comprehension*, where it is outlined that "*the person obtaining consent must ensure that the potential participant has **adequately understood the information** provided. Researchers should use **evidence-based methods for imparting information** to ensure comprehension. The potential participant's ability to understand the information depends, among other things, on the individual's **maturity, educational level and belief system**. The participant's understanding also depends on the **researcher's ability and willingness to communicate with patience and sensitivity**, as well as the atmosphere, situation and location where the informed consent process takes place*. (p. 34)"

With regard to the contents of the information leaflet that must be provided, as well as supplementary information for prospective research participants, these are presented below:

1. The purpose of the research, its methods, the procedures to be carried out by the researcher and the participant, and an explanation of how the research differs from routine medical care;
2. That the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
3. That the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;
4. The expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;
5. Whether money or other forms of material goods will be provided in return for the individual's participation, and, if so, the kind and amount, and that the time spent on the research and other inconveniences resulting from study participation will be appropriately compensated, monetary or non-monetary;
6. That, after the completion of the study, participants will be informed of the outcomes of the research in general, if they so wish;
7. That individual participants during or after a study or collection of their biological material and health-related data will be informed of life-saving information and data of immediate clinical utility involving a significant health problem;
8. That unsolicited findings will be disclosed if they occur;
9. That participants have the right of access to their clinically relevant data obtained during a study on demand (unless the research ethics committee has approved temporary or permanent non-disclosure of data, in which case the participant should be informed of, and given, the reasons for such non-disclosure);
10. Pain and discomfort of experimental interventions, known risks and possible hazards, to the individual (or others) associated with participation in the research, including risks to the health or well-being of a participant's direct relatives;
11. The potential clinical benefits, if any, expected to result to participants from participating in the research;
12. The expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;
13. How the transition to care after research is arranged and to what extent they will be able to receive beneficial study interventions post-trial and whether they will be expected to pay for them;
14. The risks of receiving unregistered interventions if they receive continued access to a study intervention before regulatory approval;
15. Any currently available alternative interventions or courses of treatment;
16. New information that may have come to light, either from the study itself or other sources;
17. The provisions that will be made to ensure respect for the privacy of participants, and for the confidentiality of records in which participants are identified;

18. The limits, legal or other, to the researchers' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
19. The sponsors of the research, the institutional affiliation of the researchers, and the nature and sources of funding for the research, and, when they exist, any conflicts of interest of researchers, research institutions and research ethics committees and how these conflicts will be managed;
20. Whether the researcher is serving only as a researcher or as both researcher and the participant`s physician;
21. The extent of the researcher's responsibility to provide care for participants' health needs during and after the research;
22. That treatment and rehabilitation will be provided free of charge for specified types of research related injury or for complications associated with the research, the nature and duration of such care, the name of the medical service or organization that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment;
23. In what way, and by what organization, the participant or the participant's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated that there are no plans to provide such compensation);
24. Whether or not, in the country in which the prospective participant is invited to participate in research, the right to compensation is legally guaranteed;
25. That a research ethics committee has approved or cleared the research protocol;
26. That they will be informed in case of protocol violations and how safety and welfare will be protected in such a case.

Vulnerable groups

Guideline 15 specifies that vulnerability involves judgments about both the probability and degree of physical, psychological, or social harm, as well as a greater susceptibility to deception or having confidentiality breached. The Guideline takes an approach where consideration of members of entire classes of individuals as vulnerable, is avoided. It is suggested that different characteristics may co-exist, making some individuals more vulnerable than others, and this is highly dependent on the context. For example, "*persons who are illiterate, marginalized by virtue of their social status or behaviour, or living in an authoritarian environment, may have multiple factors that make them vulnerable*" (p. 57).

The Guideline provides some characteristics which can make it reasonable to assume that certain individuals are vulnerable:

- Individuals with limited capacity to consent
- Individuals in hierarchical relationships
- Institutionalised persons

Special reference is made to *women* and circumstances under which they could be considered as vulnerable in various research contexts, such as studies with female or

transsexual sex workers; research on sexual and intimate partner violence; studies with trafficked women, refugees and asylum seekers; studies of abortion in jurisdictions where abortion is illegal; and research with women who live in a cultural context where they are not permitted to consent on their own behalf for participation in research, but require permission from a spouse or male relative. General considerations with regard to participation of women in research are provided in Guideline 18.

Also, according to the Guideline, pregnant women must not be considered vulnerable simply because they are pregnant. Specific circumstances, such as risks to the foetus, may require special protections, as set out in Guideline 19 – Pregnant women and breastfeeding women as research participants.

3.5 Guideline for Good Clinical Practice (GCP)

The *Guideline for Good Clinical Practice* (GCP) was released in 1996, with the aim to provide a unified standard for the European Union, Japan, and the United States to protect the rights and well-being of participants involved in clinical trials and facilitate mutual acceptance of clinical data by the regulatory authorities in these regions. Compliance with these standards provide an assurance that research participants are protected in accordance with the Declaration of Helsinki principles, and further enhances reliability for the clinical experimental data collected during the trial. The principles of the Guideline for GCP[25] are:

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

[25] The principles of ICH-GCP. Available from: <http://ichgcp.net/2-the-principles-of-ich-gcp-2>

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Informed consent

The document provides an important point in support of an approach which sees informed consent as a dynamic process. In particular, it is stated that "*The written informed consent form and any other written information to be provided to subjects* ***should be revised whenever important new information becomes available that may be relevant to the subject's consent****. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented*." (4.8.2)

Similar to other guidelines presented earlier, it is highlighted that "[…] *neither the investigator, nor the trial staff, should* ***coerce or unduly influence*** *a subject to participate or to continue to participate in a trial*." (4.8.3). In addition, emphasis is put on the need to use jargon-free language to facilitate comprehension for research participants: "[…] *the language used in the oral and written information about the trial, including the written informed consent form, should be* ***as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness****, where applicable*." (4.8.6)

Finally, the document provides further guidance on the information that may presented to prospective study participants (orally and written), as part of the informed consent process. The 20-point list (4.8.10) is presented below:

1. The trial involves research.
2. The purpose of the trial.
3. The trial treatment(s) and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.
5. The subject's responsibilities.
6. Those aspects of the trial that are experimental.

7. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
8. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
9. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
10. The compensation and/or treatment available to the subject in the event of trial-related injury.
11. The anticipated prorated payment, if any, to the subject for participating in the trial.
12. The anticipated expenses, if any, to the subject for participating in the trial.
13. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
14. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
16. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
17. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
18. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
19. The expected duration of the subject's participation in the trial.
20. The approximate number of subjects involved in the trial.

Vulnerable groups

In the section which is specific to informed consent, there is a provision regarding participation of vulnerable groups or individuals in clinical trials, specifying that "[…] w*hen a clinical trial (therapeutic or non-therapeutic) includes participants who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the participant should be informed about the trial to the extent compatible with the participant's understanding and, if capable, the participant should sign and personally date the written informed consent.*" (Section 4.8.12)

3.6 Core elements of informed consent

While the Declaration of Helsinki and the CIOMS Guidelines established the operational framework for obtaining informed consent in biomedical/health-related research, the ICH Guideline for Good Clinical Practice defined a set of standards with the aim for these to be transposed into national regulatory framework for clinical trials involving human subjects. These requirements include the responsibility of researchers to provide information about subjects' responsibilities, provide an indication about the number of subjects to be recruited, the Institutional Review Boards' or Independent Ethics Committees' direct access to medical records, and so on. All these elements are considered as necessary for participants to determine whether the research study is consonant with their interests, and therefore take a decision to participate or not (Emanuel, Wendler & Grady, 2000).

The present analysis of major international guidelines revealed that there are several elements which appear consistently as essential information to be disclosed to participants for obtaining informed consent, such as the description of the purpose of research, potential risk and benefits, the right to withdraw, and steps to ensure privacy and confidentiality (Bhutta, 2004). These core elements have been extracted and appear on Table 3, and are considered as basic information to be disclosed to participants in order to fulfil a requirement toward enhanced openness and transparency about the research study, from the part of the researcher. The question remains however: *Is this information always relevant or adequate?* And more importantly, *while basic elements of informed consent may be derived from various regulations, which of these key elements are ethically essential to being "informed"*? *How can the methods and strategies employed for the disclosure of relevant information about the research study can influence participants' understanding and capacity to process information, toward an improved informed consent?* The next sections of this report will seek to address these questions.

Table 3: Elements of informed consent (IC) required by key international guidelines.

Core elements of IC	Declaration of Helsinki	Belmont Report	CIOMS Guidelines	GCP Guideline
Identification of study as research				●
Description of research study	●	●	●	●
Expected duration of research study			●	●
Purpose/aims of research study	●	●	●	●
Explain research study vs medical care			●	
Anticipated risks and benefits	●	●	●	●
Anticipated societal benefits			●	
Right to withdraw	●	●	●	●
Potential conflicts of interest	●			
Sponsors/Funding sources	●		●	
Researcher institution affiliation	●			
Alternative procedures/interventions		●	●	●
Contact information				●
Emphasis on voluntarism	●	●	●	●
Limits of compensation			●	●
Approximate number of participants				●
Participant's responsibilities				●
Research approved by IRB/IEC	●		●	●
Steps to ensure privacy/confidentiality			●	●
Definitions			●	
Rights to access results/outcomes	●		●	
Opportunity to ask questions		●	●	●

4. Approaches for improving informed consent in clinical research

4.1 Introductory remarks

The notion of informed consent embodies the need to respect persons and their autonomous decisions. According to Emanuel et al. (2000), informed consent in the context of clinical research is a *process* aimed at: (1) providing participants with adequate information to enable them to make an informed decision as to whether to participate in the clinical research; and (2) ensuring that people participate voluntarily and without coercion in research and only when the research is consistent with their values, interests and preferences. As we have seen already in the previous section, this conceptual approach and implicit association between *adequate information* and *informed decision and/or voluntariness* has evolved with the development of international standards and requirements for the ethical conduct of clinical research.

The ICH Guideline for Good Clinical Practice provides the following definition for informed consent (1.28): "*A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been* ***informed of all aspects*** *of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form*".[26] This definition appears to support a conceptual approach where the quality of a decision is proportionate (but not limited) to the amount ("quantification") of information made available to research participants. In fact, except the ICH Guideline for Good Clinical Practice, also the CIOMS Guidelines and WMA's Ethical Principles for Medical Research Involving Human Subjects, have identified and introduced additional elements, considered to be "relevant" for participants as part of the informed consent process.

Those core elements are reflected in the informed consent form template developed by the World Health Organization (WHO), which includes the different sort of information that must be provided to research participants, and namely cover: the purpose of research, the type of intervention, participant selection, voluntary participation, information on trial drug/placebo, procedures and protocol, treatment alternatives, randomisation, additional tests/ investigations, duration, standards and guidelines, side effects, potential risks and benefits, incentives, confidentiality, sharing of results, contact information, and the right to refuse or withdraw, alternatives to participation, and contact information. Depending on the characteristics of each study, the informed consent documents can be lengthy and complicated, or have information presented in a format which offers limited understanding of technical terms (Grady, 2015).

[26] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Guideline for Good Clinical Practice (E6)R1 (1996). Available from <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf>

To reformulate a question posed earlier, *does full and complete disclosure of information prior to the study necessarily mean better decision capacity for individuals*? According to Meade (1999), there are several other factors that impact the understanding and/or comprehension of information presented in consent-related materials. These factors include level of education, presentation of content, nature of information, age, literacy skills, and cultural differences in the understanding of "risk" information. Schenker and Meisel (2011) pointed towards three practical issues that need to be considered in improving comprehension of ICDs. First, more is not always better. More information in consent forms may produce the opposite effect as participants can end up dedicating less time for reviewing the form before signing. Second, timing matters – in both clinical practice and research the informed consent process may take place immediately before a procedure, after the patient or research participant is already psychologically committed to proceed and the optimum time for weighing risks and benefits has passed.

As proposed by Rowbotham et al. (2013), understanding may be improved by providing prospective participants with several options to have the relevant information presented. If done interactively, participants can be given immediate feedback about their level of understanding of study procedures, risks, and so on, thereby theoretically increasing their overall comprehension. In addition, the comprehension level of key study elements can be verified with different techniques and tests prior to commencement of the study.

Hence, while it is important to examine informed consent as to *what* type of information is made available (or is reasonable to disclose) to participants through information sheets, leaflets and other material, it is also critical to consider *how* this information is presented and *how* different variables associated with informed consent may influence participants' decision capacity and understanding for the entire duration of a research study.

4.2 Aims

Over the past few years, and particularly after the release of the first version of the ICH E6 Good Clinical Practice (GCP) Guideline in 1996, there have been considerable efforts to improve several aspects of informed consent, from readability assessments to interventions introduced to facilitate or enhance the informed consent process.

This section offers a comprehensive review of the scientific literature with the aim to identify proposed methods, techniques strategies for improving informed consent, providing evidence-based recommendations which can serve as a basis for the future development of innovative approaches to informed consent and the formulation of guidelines, in the scope of WP2 and WP3 respectively.

4.3 Methods

The complexity of the subject presented and discussed in this report does not allow the formulation of clear research questions or hypotheses, nevertheless it requires to be

approached in a consistent and systematic way. At core, the present study is conceived as a narrative review of the scientific literature that incorporates elements of a systematic review, i.e. a clear and robust methodological framework which was set up and evolved as part of the research protocol developed in the scope of task T1.1.

4.3.1 Eligibility criteria

Inclusion criteria

The type of research studies considered were observational and experimental, while sub-population categories selected included adults, children, adolescents and vulnerable populations. The types of interventions for the review included extended discussion, enhanced form, use of multimedia (audio-visual aids), decision support techniques, and feedback collection techniques (e.g. tests, quizzes, etc.). Studies that measured and/or discussed techniques or strategies for improvement, enhancement or optimisation of the informed consent process were eligible for inclusion. Studies that investigated the above primary outcomes with informed consent under the prism of health literacy, patient education, and patient participation were also eligible for inclusion. Eligible papers were those published a peer-reviewed journal in English, available in full-text, from 1997 to 2017.

Exclusion criteria

- Studies related to obtaining IC for medical treatment. *Obtaining informed consent in clinical research is conceptually different as a process in comparison to medical treatment (including surgical interventions or treatment in emergency settings) where different procedures apply, therefore only studies focusing on clinical research were selected, in alignment with the scope of the i-CONSENT project.*
- Studies related to obtaining IC from patients with neurological or cognitive impairment. *Obtaining informed consent from patients with neurological or cognitive impairment (including patients with psychiatric disorders) requires particular technical interventions and approaches which go beyond the scope of the i-CONSENT project.*

4.3.2 Search strategy

The databases used for search of scientific papers published in peer-reviewed journals were MEDLINE (PubMed) and Google Scholar. In addition, the OpenGrey database was searched for relevant publications in the grey literature. The Mendeley reference management tool was used to keep track and store retrieved articles, and in a later phase to carry out the article screening process.

The initial search was run on MEDLINE (PubMed), with a total of 48 different combinations of keywords and/or Medical Subject Headings (MeSH) inserted, which in turn were divided in 8 different clusters. The primary subject heading used in all different combinations was “informed consent”. A narrower selection of subject headings have been used as keywords for the search in Google Scholar and OpenGrey databases, which included “informed consent” AND “improv*” OR “enhance*” OR “optimi*” AND “understanding” OR

"comprehension". Table 4 provides specific information concerning the search strategy, including the full list of keywords/MeSH and filters applied.

4.3.3 Study selection

The results from the initial search on the databases returned a total of 6,628 scientific papers, screened by *title* to identify potential relevance for the purposes of this review. The various combinations of keywords resulted in several duplicates identified at this phase. As a next step, the scientific papers were screened by *abstract* to determine if they met the eligibility criteria for this review. This process resulted in identifying a total of 193 scientific papers eligible for full text review. Another set of duplicates was removed at this stage. Discrepancies were resolved by discussion among the reviewers' team. At the end, a total of 69 scientific papers were selected and analysed for the purposes of this review.

Table 4: Search strategy for retrieval and selection of studies.

DATABASES	SEARCH FIELDS	SEARCH KEYWORDS	FILTERS
MEDLINE, PubMed	Title Abstract MeSH	**1.** "informed consent" **2.** "improv*" OR "enhance*" OR "optimi*" **3.** "clinical research" OR "biomedical research" OR "clinical trials as topic" **4.** "understanding" OR "comprehension" **5.** "minor*" OR "children" OR "pregnant" OR "paediatric" OR "vulnerable" **6.** "method*" OR "technique*" OR "strategy*" **7.** "multimedia" OR "audiovisual aids" OR "decision aids" **8.** "health literacy" OR "patient education"	English Full text available Humans Peer-reviewed journals Publication date from 01/1997 to 08/2017 (20 years in total)
Google Scholar	Anywhere		
OpenGrey	Anywhere		

4.3.4 Conceptual framework for analysis of studies

This review is a comprehensive exercise geared towards identifying and presenting methods, techniques and strategies for improving informed consent in the context of clinical research. To achieve this goal, the review was not only limited to the identification of studies which focus on methods for improving informed consent documents (ICDs), but expanded to cover any aspects associated with the process itself to overcome barriers and challenges presented in the context of clinical research.

Further to a preliminary analysis of the aims and scope of research studies selected for review, these were divided into three main clusters. First, it was found that several studies exist which concentrate on the various characteristics and technical aspects associated with shortcomings in the presentation, content and layout of ICDs, which can have an impact on participants' comprehension of the documents. Second, there is a considerable body of scientific literature that focuses on the role and use of multimedia as an intervention to

introduce as a complementary component in the process for improving understanding and/or better retention of information presented. Third, a number of research studies focus on the process itself, presenting different approaches for enhanced and effective communication between researchers and participants.

Indeed, while it is of importance to identify and address issues related to the content and presentation of ICDs, informed consent is all about communication and there are various, contextual parameters or situational factors that need to be considered, as these can influence the quality of decision taken by participants to enrol (and fully participate) in a research study. The study by Lorell et al. (2015) highlighted this need to consider all different parameters and factors toward enhancing research participant understanding in clinical research, which are presented in Fig. 2.

The following sections present key outputs and considerations from research studies relevant to informed consent in the context of clinical research. Core issues and findings are discussed, followed up by evidence-based recommendations.

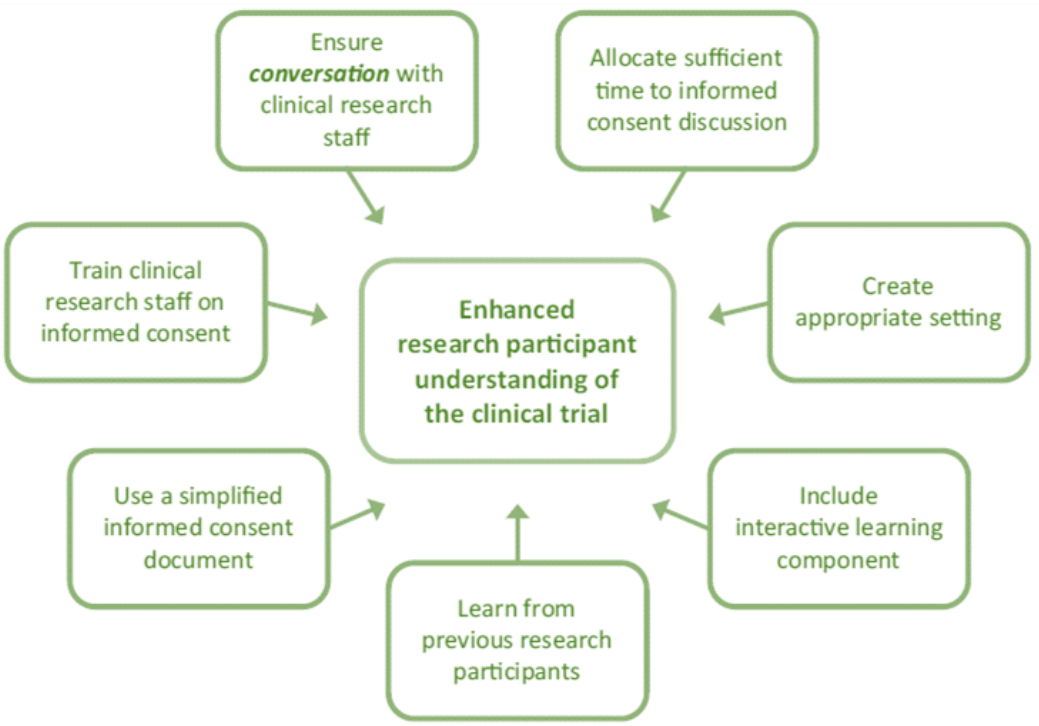

Fig.2 - Enhancing research participant understanding of a clinical trial

Taken from B.H. Lorell, J. S. Mikita, & A. Anderson (2015).

4.4 The case of informed consent documents (ICDs)

Informed consent documents (ICDs) serve as the means for disclosure of all necessary (or relevant) information about the research study, in addition to the information provided (orally or visually) by researchers, in support of the decision-making process. Guided by the

Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice (GCP) Guideline, the WHO Research Ethics Review Committee (ERC) presents as a point of reference various types of informed consent form templates, which consist of two main parts: the *information sheet* (Part I) and the *consent certificate* (Part II). The sections that comprise Part I are representative of the core elements introduced and discussed across the available international guidelines for informed consent in clinical research and trials.[27] The list of information that need to be covered for the information sheet to be considered as complete, are as follows:

1. Introduction
2. Purpose of research
3. Type of research intervention
4. Participant selection
5. Voluntary participation
6. Information on the Trial Drug [Name of Drug]
7. Procedures and protocol
8. Unfamiliar procedures
9. Description of the process
10. Duration
11. Side-effects
12. Risks
13. Benefits
14. Reimbursements
15. Confidentiality
16. Sharing the results
17. Right to Refuse or Withdraw
18. Alternatives to participating
19. Who to contact

The *Informed Parental Consent Form Template for Research Involving Children (Clinical Studies)*[28] includes an additional element, entitled "Discomforts", the purpose of which is to explain and describe the type and source of any anticipated discomforts that are in addition to the side effects and risks discussed in those sections

ICDs are often criticised for their excessive length, poor organisation/structure, and complex language that exceeds the reading ability of an average person (Albala, Doyle & Appelbaum, 2010; Jefford & Moore, 2008; Grady, 2017). As we have discussed in the previous section, a possible reason for this noted increase in length and complexities presented in ICDs are the gradually more stringent regulations with regard to disclosure, with implications for the level

[27] WHO ERC Informed Consent Form Template for Clinical Studies. Available from <http://www.who.int/rpc/research_ethics/informed_consent/en/>
[28] WHO ERC Informed Consent Form Template for Clinical Studies. Available from <http://www.who.int/rpc/research_ethics/informed_consent/en/>

of comprehension and understanding of relevant information, which are pre-conditions of informed consent of information for prospective research participants (Berger et al., 2009; Brehaut et al., 2010).

Dellson et al. (2016) explain that shortcomings related to the content and presentation of information in ICDs can be attributed to the fact that such material are generally developed by medical professionals and researchers, whose focus is more on *what* needs to be presented as information rather than *how* this information is presented. However, the importance of learning *how* to write in a functional and consistent manner, and not simply focus on *what* content to convey should never be underestimated (Sand, Eik-Nes & Lodge, 2012). Even participants with health literacy skills can find difficult to understand some information presented in standard informed consent forms and related materials (Paasche-Orlow et al., 2013).

This section discusses various aspects and issues related to ICDs, as these emerged from the literature review, which determine to a significant extent the ease of readability and comprehension of information presented. Based on the outcomes from the review, four key parameters have been identified as relevant for the improvement of ICDs: (a) Content, (b) Length, c) Features, and (d) Structure. These are discussed separately, followed by a set of considerations and recommendations for improvement.

4.4.1 Content

While there is consensus that ICDs should be written at or below an eight-grade reading level (Denzen et al., 2012), a number of recent studies have shown the readability of an average consent document is often above the recommended level. Specifically, a study by Vučemilo and Borovečki (2015) evaluated the level of reading difficulty for 52 informed consent forms from six Croatian hospitals on the secondary and tertiary health-care level. For the purposes of the research, the Simple Measure of Gobbledygook (SMOG) formula was used to assess difficulty of content by the number of polysyllabic words. It was found that evaluated informed consent forms were written for an educational level considerably higher than the majority of Croatian population. Similar results were obtained by Koyfman et al. (2013), which showed that readability of an average informed consent document was above a 10^{th} grade reading level, with technical jargon and inconsistent use of medical terms used in many of the cases. There is research to suggest that better results can be obtained with ICDs lowered to the sixth-grade reading level (Donovan-Kicken et al., 2013, Lorenzen, Melby & Earles, 2008). It has been shown that by having the reading level reduced and the length of consent documents shortened, this can have a positive impact for participants and their ability to describe procedures in their own words (Lorenzen, Melby & Earles, 2008).

Another issue related to readability and content of ICDs is the inclusion (or lack of) of basic elements considered as minimum requirements in clinical research studies, in adherence to the Guidelines for Good Clinical Practice and other international guidelines, such as the Declaration of Helsinki and the CIOMS Guidelines. Vučemilo and Borovečki (2015) found in

their study that content of examined ICDs failed to include in high proportion of the cases description of: *alternative treatments and procedures*, *benefits of alternative treatments and procedures*, as well as *risks and benefits of not receiving treatments or undergoing procedures*. In another study by Wen et al. (2016) it was revealed that informed consent forms had poor description of *alternatives to participation*, and failed to provide a high degree of information disclosure, including an explanation of informed consent, follow-up processing of the data, inclusion/exclusion criteria, double-blinding and unpredictable risks.

A study which analysed a total of 300 ICDs submitted for evaluation to the Institutional Ethics Committee of India also revealed that in several occasions core elements were not up to standards, such as *information about alternatives to study participation*, *potential risks and benefits*, and *contact information* about the research team (Padhy, Gupta & Gupta, 2011). An analysis of ICDs in Norway over a period of 20 years, also revealed that only a small number of documents provided *reasons to leave the trial*, *inclusion/exclusion criteria*, *participants' responsibilities*, *possible disadvantages/advantages* and *side effects* (Sand, Eik-Nes & Loge, 2012).

A study by Lorell et al. (2015) revealed concerns about excessively lengthy and detailed information related to required disclosures of "procedures to be followed in the study", "any benefits to the subject or to others which may be reasonably be expected from the research", and "any reasonably foreseeable risks or discomforts to the subjects". An interesting point was made in the scope of this study about the need to be selective in the content provided, providing more elaborate information for risks that are more likely to occur. This is actually a recommendation by the US Food and Drug Administration (FDA), which suggests that: "[…] *All possible risks do not need to be described in detail in the informed consent form, especially if it could be overwhelming for subjects to read. Information on risks that are more likely to occur and those that are serious should be included*".[29]

4.4.2 Length

Length and density of text can have an adverse effect on participants' desire and willingness to completely read the consent form (Davis et al., 1998). According to Sharp (2001), people are not willing to spend much time reading consent forms, and they are likely to read no more than four pages (approx. 1000 words) of an informed consent form. Consent documents often contain ten or more pages of single-spaced text which can be daunting participants, however study results are largely inconsistent as to whether this component alone can have a major impact for improving participants' understanding (Sharp, 2001).

Another study by Stunkel et al. (2010) evaluated the effect of a shorter and simpler consent form on the comprehension and satisfaction of research participants. They concluded that the longer consent form did not generate greater comprehension, and the concise form did not enhance satisfaction. The main finding was that neither comprehension of study

[29] US Food and Drug Administration. Informed consent information sheet. Available from : <https://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm>

information nor satisfaction with the consent process was affected by either the length or the complexity of the consent form. It was found that volunteers had the same level of comprehension after reading a 14-page or a 4-page consent form.

Sand et al. (2012) also demonstrated that longer ICDs are not necessarily less readable, provided that these are logically organised and more thematically adequate. Paris et al. (2015) found no significant difference between a very short (5 pages) and a much longer (11 pages) consent document in terms of comprehension and final enrolment. Instead, they improved readability by reducing the length of words by using short synonyms and reducing the length of phrases. These findings are in line with study by Davis et al. (1998) who found that readability of consent forms was improved by changes that included shortening the title, reducing the length of the text and simplifying the language.

Wen et al. (2016) examined for readability a total of 155 consent documents from phase II-IV drug clinical trials. These were evaluated in terms of length, readability and content. The readability assessment was based on an analysis of a) text length, b) font size, c) number of pages, d) presence of a flow chart, and e) use of appropriate sub-headings. The analysis showed that the length of consent documents can influence the level of engagement of readers with the text and information presented, so it is proposed to keep ICDs as concise and succinct as possible (approximately 4200 characters/6 pages).

An older study by Dresden and Levitt (2001) compared a standard, industry consent form and a modified, shortened version of the same form to determine which of the two versions allows the patient to retain more information in the immediate post-consent period. Several features that have been reported to increase readability were incorporated into the design of the form, such as shortened headings; bullets; bold, underlining, italics, and increased font size to place emphasis on important words such as “if” and “voluntary”; more lay vocabulary and sentence syntax. Patients who received the modified consent form (i.e. short version) had better performance as far the retention of information was concerned.

4.4.3 Features

The majority of studies reported in this section point to the lack of graphic elements or illustrations in support of information presented in ICDs assessed for readability (Meneguin & Ayres, 2014; Sand, Eik-Nes & Loge, 2012; Vučemilo & Borovečki, 2015; Wen et al., 2016). Several studies have shown that graphical elements, diagrams, pictures and bullet points facilitate processing and enhance understanding of information, independently of the health literacy level (Hawley et al., 2008; Kim & Kim, 2015; Tait et al., 2010). The theory behind this observation may be grounded on the so-called *pictorial superiority effect* (PSE) which posits that information provided in pictorial format is easier to understand and requires less cognitive effort compared with text (Nelson et al., 1976).

In a systematic review carried out be Nishimura et al. (2013), the enhanced format was identified as an effective approach for improving informed consent, with a focus on revised layout, text styling and added pictures. The study by Dellson et al. (2016) also supported the

need for ICDs to include an attractive layout and contain illustrations and graphical elements, which represent the preferred mode of information for many individuals, as well as the need to follow a logical structure for their ability to understand the contents.

4.4.4 Structure

Readability of ICDs is also dependent on the structure, i.e. information presented coherently in a logical order. According to Nystrand (1986), the information written in the beginning of a document forms the basis for the reader's interpretation of the rest of the information. Dellson et al. (2016) support the view that first impression of a text is pivotal in participants' decision and motivation to continue reading and to assimilate information presented in the text.

To better guide the reader, a writer needs to consider which topics might be the most appropriate to place in the beginning, the middle and the end of the document. Sand et al. (2012) offer another perspective, which suggests that a document can be considered as "readable" when the reader knows what to do with the information presented – merely read it and comprehend it, or act upon it. While the order of themes is important to enhance readability for ICDs, the consideration of rhetorical functions can help the reader to better engage with the information presented in different section of the document. The most frequent rhetorical functions in relation to ICDs are: (1) *to inform*, i.e. to present facts and implications regarding the reader's diagnosis and treatment, the clinical trial and the implications of participating; 2) *to explain*, i.e. to provide explanations immediately after information presented; 3) *to instruct*, i.e. to give reader instructions about what to do in the trial, participants' responsibilities and how to give consent; 4) *to ask*, i.e. invite the reader to ask questions throughout the process.

The study by Sand et al. (2012) outlines five best practices for designing ICDs which are both consistent and functional:

1. Emphasise research as main topic in the ICD, i.e., present the request to participate, the study procedures, the choices the reader has, the implications of choosing one or the other, the reader's rights. Patients may want a lot of information about their disease, treatment, and prognosis. In the consent process, however, all of this information should be framed as part of a research setting in order to be functional.
2. Emphasise the request to participate as main function. The information in ICDs is related to some clear actions, first and foremost the act of consenting. This might be clarified by placing a request in the beginning of the information, by repeating the request, and by giving the reader clear instructions about how to proceed if he/she wants to consent.
3. Clarify the relationship among the reader, the writer, and any additional actors in the document. This might be done by clarifying the dual roles of the involved persons, e.g., making it clear that the physician is also an investigator. The actions the different

persons are supposed to perform might be clarified by writing in the active voice and including subjects in the sentences.

4. **Orient the ICD towards the target reader**, i.e., the eligible trial participant, not only a "patient," and not towards the ethics review board.
5. **Explain expert terms; do not avoid them.** Since ICDs often are supposed to give the reader information about complex medical research, expert terms might be necessary in order to make the information sufficiently precise. To clarify for the reader, it is necessary to explain in lay terms.

4.4.5 Recommendations

The following recommendations for improving ICDs have been collected and distilled from the presented studies and associated outcomes from readability assessments carried out across different countries.

PARAMETER	RECOMMENDATIONS
Content	• Use simple words/language • Avoid unnecessary words and technical jargon • Define technical words or provide a glossary of terms • Explain medical terms • Be consistent in the use of words and terminology *e.g. use the term "study" throughout the entire document vs using a combination of terms such as "study", "investigation", and "research"* • Write in the active voice; use a conversational style. *e.g. state "You are being asked to take part in a study about…", instead of "Patients are being asked to participate in a research investigation designed to…"*
Length	• Use short sentences • Avoid polysyllabic words *e.g. use "take part in" instead of "participation", use "now" instead of "immediately", use "needed" instead of "clinically indicated"*
Features	• Use graphic elements and illustrations • Involve professional writers, illustrators • Provide generous white space • Use a minimum of 12- to 14-point type of text; use 16- to 18-point type for headers; type size may need to be adjusted depending on visual needs • Use numbering and bullets
Structure	• Introduce purpose of study early in the document to frame the message

	• Convey elements of informed consent in a logical, organised manner. • Use headers to introduce the elements of informed consent and to break up the text • Subheadings should cover/correspond to the subsequent content
Other	• Do consider participants' cultural aspects language preferences • Know the target audience • Pilot the consent document with patients for ease of reading, clarity and understanding.

4.5 Informed consent and the role of multimedia

As discussed previously, a main challenge in the process toward obtaining genuinely informed consent is the noted increase and complexity of information presented in recent years with respect to traditional versions of ICDs. The presentation of ICDs in the traditional format was intended primarily to provide liability protection to providers, so it was inevitable to some extent for these documents to include complex medical and legal terminology (Matiasek and Wynia, 2008; Paasche-Orlow et al., 2003). Except from proposed techniques to enhance the reading ease and increase comprehension of related material and procedures, alternative methods have been examined to present these information with the use of multimedia and other interactive tools as part of the process.

ICDs available in electronic format can be considered as an advancement in the field of clinical research. Electronic versions of traditional ICDs (e-consent forms) are not only limited to standard information and advanced graphics or illustrations, but make use of multimedia and interactive computer interfaces, which can increase comprehension about several aspects of the study, particularly for people with a low educational level or limited literacy (Rowbotham et al., 2013; Tait & Voepel-Lewis, 2015). Although barriers still remain in the adoption of e-consent (e.g. concerns about security or confidentiality, lack of well-established processes, initial development costs, and global acceptance of e-signatures), the advantages seem to outweigh the concerns (Lentz et al., 2016). Studies have demonstrated that e-consent is superior to traditional consent processes using metrics such as: 1) study participants' comprehension of information presented in the informed consent documents, 2) study participants' satisfaction with decision-making and the informed consent process, 3) retention of study participants, and 4) protocol compliance by study participants (Nishimura et al., 2013; Rowbotham et al., 2013).

The use of multimedia for the delivery of study information during the informed consent process received some criticism as it may weaken compassionate human interactions that form the basis of research ethics (Rosoff, 1999). However, this criticism had been in the context of using multimedia not as supplementary tools, but rather as a substitute of key parts in the process which involve face-to-face interaction with the researcher. As pointed out by Rosoff (1999), it can be counter-productive to depend solely on the technology to meet

the information needs of participants during the informed consent process, so there is a need to find the right balance between use of multimedia and human interaction.

Same as the traditional ICDs, electronic informed consent presents challenges in relation to key components such as, disclosure, understanding, voluntariness, and authorisation. A study by Grady (2017) summarises the main challenges associated with traditional and electronic consent (Table 5). There is still distance to cover before the use of multimedia and interactive tools can be considered not simply as interventions for the replacement of traditional ICDs, but as the solution to overcome present barriers in the communication process. As noted by Grady (2017) "*Replacing long, complex, technical written forms with long, complex and technical or legalistic electronic information pages would not represent progress*".

An earlier study by Karunaratne et al. (2010) assessed the efficacy of a computer-based approach to communication about complex, technical issues that commonly arise when seeking informed consent in clinical research trials. The intervention used involved two groups of participants reading information about a mock study via a computer-based presentation, or a conventional paper-based information statement. The computer-based presentation contained visual aids, including diagrams, video, hyperlinks and quiz pages. Results showed that a computer-based approach to communicating information about clinical research to prospective trial participants can improve the consent process, compared with a conventional approach using a paper-based statement.

Table 5: Components and challenges of IC with traditional paper and electronic methods *(Adapted by C. R. N. Grady, 2017)*

Component	Traditional paper IC	Electronic/Digital IC	Challenges and areas of research
Disclosure	- Information is written, usually on paper - Discussion with investigator takes place, usually face to face	- Consent can involve electronic information, multimedia information, video graphics, and interactive computer interfaces - Investigator can be remote in time or place from participant	- All types of disclosure require determining the appropriate content (amount and complexity of information) for disclosure - User friendly disclosure is needed - Amount and style of information tailored to electronic platforms need to be determined
Understanding	- Investigator and participant discuss information - Participant asks questions - Investigator assesses understanding, in some cases using questions, structured quizzes, other methods	- Interaction can take place during disclosure - Questions and assessment of understanding are easily built in - Ongoing engagement is enabled - Links to additional information	- Evidence indicates that people do not read click-through agreements on computers and mobile devices - Information should be engaging and user-friendly to promote reading and understanding - It may be difficult to assess capacity and understanding

Voluntariness	- Investigator asks participant to make a choice in a setting free from coercion and undue influence - Research team observes participant's body language and any hesitation	- Some electronic systems facilitate participant control - Participant can easily sign off or disengage - Participant can decline	- It may be difficult to assess voluntary choice without the clues of body language and tone - It may be difficult to verify the identity of the person consenting - Some data collection is passive - In some cases, contributing data is a required part of the arrangement
Authorisation	- Paper consent document is signed - Copies of document are kept in records	- Options might include clicking agreement or an electronic signature - Records of agreement are kept electronically	- It may be difficult to verify the identify the identity of the authorising person

4.5.1 Conclusions drawn from systematic reviews

Flory and Emanuel (2004) performed the first systematic review to investigate the effect of multimedia interventions in the informed consent process. Their conclusion was that there is no practical evidence to support that such interventions can enhance understanding, indicating that further research is needed with multimedia tools to determine best deployment, as some of the reviewed studies had been identified to be of poor quality. From a total of 12 clinical trials which used multimedia interventions (computer or video in place of or in addition to the written ICDs), only three significantly increased understanding. It was concluded that for most of the trials of enhanced consent forms that showed a significant effect, the simulation of the consent process was unrealistic in that there was no active discussion, only a reading of the form. The most effective way to improve understanding and the consent experience as a whole, was based on interactions with participants during the process, via tests/quizzes and/or feedback.

In a systematic review by Nishimura et al. (2013), a total of 54 interventions and meta-analysis of 22 interventions were investigated to evaluate effectiveness of methods used for improving rates of participant understanding in the informed consent process. The findings suggested that enhanced consent forms and extended discussions were most effective in improving participant understanding. Multimedia interventions were found to be effective, but not significantly so, and appeared to be more useful for improving long-term knowledge retention rates. Interventions involving test/feedback quizzes may be effective, but according the authors the available studies were too sparse to draw any useful conclusions. At the same time, another study by Palmer et al. (2012) reported that for half of the studies reviewed (10 out of 20) the comprehension of information was improved as a direct outcome multimedia consent tools that were used. It was concluded that the consensus is that the value of multimedia consent tools is promising but remains unclear.

In a Cochrane systematic review by Synnot et al. (2014), the main question sought to answer was: "*Does audio-visual presentation of information for informed consent for participation in clinical trials improve outcomes related to the informed consent process?*" The authors conducted an exhaustive review of studies published up to June 2012. The review included 16 randomised controlled trials. Interventions included the presentation of simple audio-visual interventions, such as non-interactive videos, viewed independently, to computer programs with quizzes and hyperlinks, viewed under supervision. Many audio-visual interventions included additional elements, such as written materials and/or face to face explanation.

Similarly, to other systematic reviews, it was found that there is still much uncertainty about the effect of audio-visual informed consent strategies on a range of patient-important outcomes. From the review it was unclear which elements of audio-visual presentation are the most important to include (e.g. interactivity, whether they can be watched alone or need supervision, whether they should be accompanied by written materials). Synnot et al. (2014) stressed that there is low quality of evidence to support the claim that audio-visual informed consent interventions may slightly improve knowledge or understanding, or improve satisfaction with the information provided. These results are consistent with an earlier study by Ryan et al. (2008) which examined the effects of providing audio-visual information for patients considering participating in clinical trials, alone or in conjunction with standard forms of information. The value of audio-visual interventions could not be determined as the findings from this study have been inconclusive about any significant improvements in comprehension as a result of these interventions.

4.5.2 Context-specific use of multimedia

Despite the lack of clear evidence from systematic reviews about the positive impact and overall effectiveness of multimedia interventions introduced as part of the informed consent process, there is a number of recent studies which examined the use of multimedia in specific contexts.

The study by Kass et al. (2011) highlighted the need to adopt a mixed-format approach when information is presented to participants, and depending on the selected format (electronic or paper-based) the content could be tailored accordingly to minimise distraction from information that really matter to participants. For example, it was suggested that information about privacy and confidentiality, while legally required, is cumbersome and distracts research participants from understanding the requirements of study participation. The mixed-format approach was also tested by Rowbotham et al. (2013), who demonstrated that combining an introductory video, standard consent language, and an interactive quiz on a tablet-based system improves comprehension of research study procedures and risks.

Sonne et al. (2013) developed a series of video clips for use during the consent process to better explain research procedures to potential participants. These videos were supplementary to the written consent. The majority of participants preferred the video-assisted consent to the paper format. Specifically, video assistance was found to be helpful

when describing procedures, as opposed to explaining conceptual aspects of study participation, such as randomisation and de-identification. Those who preferred paper did so mainly because they wanted to have the option of going back to re-read portions of the consent. The authors also suggested that video-assisted consent may help minimise therapeutic misconception as it can give participants a better understanding of what to expect in the trial.

The study by Hoffner et al. (2013) also concluded that participants watching a video clip is clearly beneficial to the process. According to their findings, patients reported that the video fostered valuable communication with the health care team about the clinical trial, thus enhanced the overall informed consent process. Based on patients' feedback, the video was also helpful to family and friends, in enhancing their understanding of clinical trials and accepting their decision for participation in clinical trials. As stated by the authors, the use of video-recorded information can serve as a tool for providing answers to questions and further ease the burden for the patient who would like to describe clinical trials to his/her close environment.

An important outcome from this study was that participants did not consider the information presented in the video clip as a critical parameter for their decision to participate in the study or not. Parameters reported to have had a greater impact for patients' decision to participate in the trial, included prior expectations about the research study, influences of their referring physicians, and conversations with the researcher and the team. For those patients who reported that the video clip had some effect on their decision to participate in the trial, there were more than twice as many men (40%) who found that this video helped them in deciding to participate, compared to women (19%).

The study conducted by Calderon et al. (2007) revealed that minority populations with low health literacy were generally more open to visual multimedia based information (Calderon et al. 2007). Lakes et al. (2012) reported that minority focus group participants expressed a desire for more detailed information in various formats (such as brochures, FAQs, and DVDs) to increase the "legitimacy" of the research. Bickmore et al. (2009) tested the use of a computerised avatar for information delivery and found that the animated computer agent had been more successful in getting participants to understand and proceed with signing the consent forms, than a human agent. Participants with limited literacy, however, did poorly on comprehension across treatment conditions.

George et al. (2013) tested the effectiveness and acceptability of an animated video to enhance health literacy among minority multicultural populations. They found that after viewing a video which was of educational purpose, based on a story of four work colleagues sharing their curiosity, reservations, and knowledge about health research participation. After viewing the video, participants appeared to be able to identify gaps in their own knowledge about health research and to express an increased desire to seek information to address these gaps. More precise questions regarding the risks, or the role of placebo in clinical trials. Interestingly, female participants worried more about the personal physical risks than did

male participants. Such concerns may stem from the women's greater need to take into consideration the needs and opinions of their families when making such decisions. Another finding that supports the importance of decision making in minority populations was that after viewing video the participants across all ethnic groups reported feeling positive about being able to give or receive family support throughout the research process.

A study by Tait et al. (2015) compared parents' and children's understanding of clinical trial information delivered using either an interactive multimedia program or a traditional paper format. The approach used entailed the presentation of information in both visual and written formats, together with a narrative "voice-over". It also included a series of exercises, in contrast to the paper version format, which contained text identical to the digital version. Results from the study showed that children that used the interactive program had significantly greater comprehension of trial concepts and participation compared with children receiving the traditional paper format. Furthermore, data suggested that interactive programs enhance understanding because they promote active learning. The use of exercises with corrected feedback showed to be effective in promoting retention of information. These findings are supported by earlier studies which found that multimedia formats can enhance comprehension in the research informed consent process, and participants, including children, express preference for multimedia over written formats (Palmer, Lanouette & Jeste, 2012).

Another study by which aimed to investigate effects of audio-recorded information on knowledge and understanding in patients considering participation in a clinical trial, showed no significant effect on knowledge or understanding (Bergenmar et al., 2014). Nonetheless, an earlier study by Lloyd et al. (2008) demonstrated the acceptability of using audio-recorded patient information sheets and obtaining informed consent via audio-recordings in minority ethnic groups where there may be difficulties with literacy.

In conclusion, the studies about the impact and benefits of multimedia use in the informed consent process have not produced any consistent results regarding their effectiveness in improving participants understanding of information presented in the context of clinical research. Despite these uncertainties, there are research studies to support use of multimedia as supplementary to other information material made available to participants. A clear benefit for the use of multimedia in relation to some information presented by researchers for explanation of different aspects of the study, is the possibility to provide consistently the same research information to all participants in the same manner. According to Afolabi et al. (2014), such type of multimedia interventions can remove any inter-person variations in the presentation of informed consent information, which can be important for specific groups such as those with low health literacy skills.

4.6 Methods for improving the informed consent process

There is a growing body of evidence that suggests the informed consent process does not fully satisfy the needs of clinical research participants (Flory & Emanuel, 2004; Meade, 1999, Nishimura et al., 2013). Brehaut et al. (2010) identify three primary problems or barriers to improve informed consent. First, evidence from empirical work has emphasised improvements in documentation rather than the process of decision making. While clear documentation serves a variety of useful purposes, it is insufficient to support adequately informed decisions (Brehaut, Saginur & Elwyn, 2009). Second, most efforts to improve informed consent involve ad-hoc interventions that lack any theoretical foundation. Third, there has been a lack of clarity around the normative standards – and hence, appropriate measures – for comprehension.

A systematic review conducted by Falagas et al. (2009) examined informed consent process in clinical research on the basis of a number of components which reflect core elements presented in ICDs: (1) *comprehension of the aim of the study*; (2) *evaluation of the amount of given information*; (3) *understanding of the concepts and procedures of randomisation, voluntarism and study withdrawal*; (4) *comprehension of the risks and benefits of participating in clinical research study*; (5) *understanding of the degree of therapeutic misconception*; and (6) *understanding of alternatives to treatment in the case of not participating in the clinical trial*. The study revealed that risks and benefits of participation, as well as alternatives to treatment appeared to have been comprehended by a relatively small number of participants in clinical trials. This is an interesting finding since as we have seen earlier in the report, the readability assessments of ICDs revealed that in many occasions these elements were found to be missing from information presented to prospective participants. In addition, participants entering a clinical trial seemed to expect substantial benefit to be conferred by the novel treatments.

It is not uncommon for participants to enter clinical studies without understanding basic principles of the research. As noted by Brehaut et al. (2010), "[…] *variability in the extent to which people understand the studies in which they are participating is almost certainly the norm, with many participants not understanding enough to satisfy even liberal interpretations of informed consent*." (p. 219). Even when consent forms have the requisite information, that information is not transmitted to the participants in any meaningful way under standard informed consent processes (Brehaut et al., 2010).

4.6.1 Informed consent: A dynamic and continuous process

A common misconception about informed consent is that it is considered as a one-off event, limited in the boundaries of disclosing relevant information and providing comprehensive explanations, so potential participants can decide whether to enrol in a study or not. However, the process of informed consent does not end there; obtaining informed consent is a dynamic and continuous process. The conceptual framework of continuous consent is based on the principle that participants should be kept aware of information relevant to their

continued participation. This type of consent occurs subsequent to participants' initial enrolment, and in settings where no substantial changes have occurred to the study that would warrant obtaining their re-consent, in which "significant" changes to research are presented and documented by an impartial witness.

Initially, this concept of continuous consent was introduced in a study by Allmark and Mason (2006), which explored methods for improving the quality of consent, to effectively tackle any issues that could threaten its validity due to various issues or challenges that can emerge at different stages of a study. Smith et al. (2011) examined how such an approach could be applied in the clinical research context. According to the authors, it is reasonable to implement such an approach considering that participants may forget relevant information over the course of their participation, such as the right to withdraw (Wendler & Rackoff, 2007).

Smith et al. (2011) state that continuous consent can be implemented by incorporating into clinical trials periodic and informal discussions. Specifically, it is suggested that as the study develops, researchers may briefly discuss with participants: 1) up-coming aspects of the study; 2) any changes to participants' circumstances or the study; 3) the importance of the study; 4) the importance of continued participation; 5) participants' right to withdraw. According to Smith et al. (2011), by adopting such an approach to informed consent, it could provide participants with an explicit opportunity to ask questions and raise any issues which have become relevant only after they have agreed to participate.

Changes also may occur after participants have enrolled to a study. New options may become available, participants' health may decline and so on. The question posed by Smith et al (2011) was whether the standard informed consent process is sufficient to keep research participants informed over time about aspects of the study relevant to their on-going participation. This question could be answered by looking into the understanding and desire for information of individuals who were participating in a longer-term clinical trial. Their study across three different countries (Argentina, Brazil and Thailand) provided evidence that there is indeed a need to keep participants informed during their participation in the trials, for longer-term trials should consider a process to ensure that participants remain informed over time about aspects of the study relevant to their participation.

4.6.2 The "cognitive interviewing" method

A few years back, Willis (2006) introduced the *cognitive interviewing* method in the context of clinical research, as a tool for improving the informed consent process. This entailed a proposal for researchers to adapt cognitive interviewing as a means to assess the understandability of consent materials and the way in which participants use this information to make decisions about their involvement in a research study.

Cognitive interviewing was developed as a formal method in the 1980s, as part of a collaboration between cognitive psychologists and survey researchers known as CASM (Cognition and Survey Methodology). The CASM approach emphasises the fundamental

contribution of cognitive functions for information processing to the task of responding to survey questions. Cognitive interviews rely on the 4-Stage cognitive model:

Table 6: Stages of the survey response process (*Adapted by Tourangeau, 1984*)

1.	*Comprehension* of the question
2.	*Retrieval* from memory, or recall, of information that question enquires about
3.	*Decision/Judgement/Estimation* processes, especially concern the adequacy of answer
4.	*Response*, in which the respondent attempts to match an internally generated answer to the response categories provided or expected by the investigator

The CASM approach is based on the notion that survey questions and other materials fail due to problems encountered in the information processing chain. As a tool, cognitive interviewing examines this processing chain and identifies the source of the problem with respect to the evaluated materials. As such, an item may present comprehension problems because it is too lengthy to be encoded; or it may request information that the respondent can no longer remember (Willis, 2006). Cognitive interviewing is characterised by the use of verbal probing, which is a common technique employed to enable participants to articulate their concerns (see also Wade, 2009). This demands active, directed investigation by the interviewer. Verbal probes can be proactive, developed prior to the interview based on the anticipation of problems; or reactive, and administered because the participant has provided some indication of difficulty (Willis, 2006).

The paper continues to suggest that as an overall objective, it may be particularly valuable to apply cognitive interviewing techniques to learn how potential subjects comprehend the terms commonly used by researchers in the consent process, as particular words may convey complex denotative and connotative meanings (Butters, Sugarman & Kaplan, 2000). The study by Hochhauser (2003) identified a range of *concepts words* used in consent forms that are likely to be misunderstood because they describe general ideas, abstract concepts, or references. Some of the examples provided include: "*assigned by chance*", "*at risk*", "*sponsor*", "*clinical condition*", and "*retrospective study*". Further, problematic *category words* are identified that describe groups of concepts: "*abnormal laboratory tests*", "*my legal rights*", and "*unexpected toxicities*"; as well as *value judgment words* such as "*absolute confidentiality*", "*rare occasions*", and "*serious medical events*".

Willis (2006) continues to suggest that in order to evaluate the extent to which these terms are problematic or not, researchers/investigators can probe term comprehension; e.g. "*What do you think we mean by a 'clinical condition'*?" Hochhauser (2003) also provides examples of modified wording presumed to be both simpler to understand and more specific (e.g. "*assigned by a coin toss*" as opposed to "*assigned by chance*"; "*swallow a pill*" instead of "*oral administration*"; "*your name and address*" rather than "*identifiable information*"). As a precedent, Butters et al. (2000) analysed the transcripts of in-depth interviews conducted

with 26 former medical research participants to determine their interpretations of common phrases such as "*clinical investigation*" and "*medical experiment*". The former term was found to present confusion and inconsistency, and the latter produced pronounced negative connotations.

Another key point made by Willis (2006) is that the cognitive interview cannot only be conceptualized as a means for the development and pretesting of consent materials, but also as a method by which participants' cognition can be assessed at multiple points during the course of the ongoing investigation. This is consistent with the discussion points presented in the previous section about the need to consider informed consent as a continuous process, with embedded techniques to evaluate and ensure understanding of different elements associated with research for the duration of their participation in the study. Embedded cognitive probing techniques can turn an otherwise largely one-way delivery of information (investigator-to-subject) into a bidirectional exchange with built-in means for identifying misinterpretations (Willis, 2006).

4.6.3 Teach-back and teach-to-goal methods

A review conducted by Tamariz et al. (2012) with the aim to evaluate available evidence supporting interventions to improve the informed consent process in low literacy populations, found that the most effective interventions for improvement in comprehension had been the *teach-back* or *teach-to-goal* methods, which involved extended discussions between the researcher and the participants.

The teach-back method is the practice of asking prospective participants/patients to discuss in their own words their understanding of what they have been told by the researcher/medical professional. This method aims at assessing comprehension and identifying gaps in participants' understanding with regard to information presented or the process itself. Prior to signing the consent documents, a question such as, "Can you tell me about the purpose of this study, in your own words?" could reveal what a prospective participant knows and does not know – perhaps more effectively than a general enquiry such as, "Do you have any questions about the study purpose?" And beyond the initial informed consent process, the teach-back approach can be considered as a way to support an ongoing consent process and participant comprehension of procedures conducted during the study.

The teach-to-goal method is the practice of asking prospective participants to describe the research procedures or to answer questions about the study, after they have read the consent form. Misperceptions are corrected, and the participant's comprehension is assessed again. Those who cannot demonstrate comprehension after several attempts are excluded from the study (Ahalt et al., 2017). This method is also used with populations at disproportionate risk for comprehension-relevant vulnerabilities, such as low literacy. Sudore et al. (2006) demonstrated the effectiveness of the teach-to-goal method in a descriptive study which aimed to determine whether literacy and demographic characteristics are associated with understanding consent information. Use of this method was successful in

achieving complete comprehension in 98% of all participants who engaged in the consent process, including those with literacy or language barriers.

In essence, teach-back method and teach-to-goal method start as a process with a new concept or new piece of health information and then uses an iterative process to achieve and assess understanding. This process has been represented schematically by Schillinger et al. (2003), as illustrated in Fig. 3.[30]

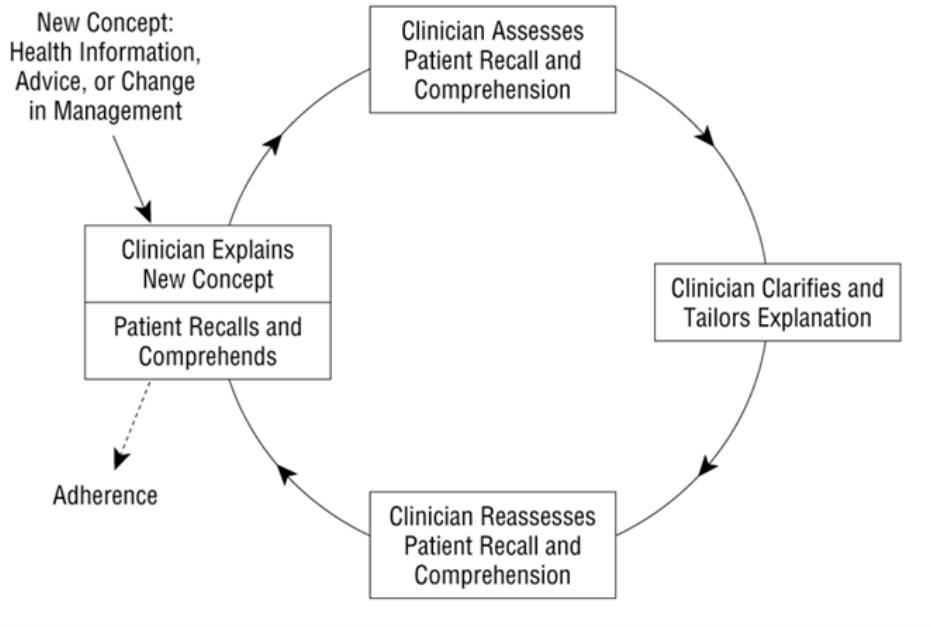

Fig. 3: The cyclical process of teach-back and teach-to-goal methods

(Taken from D. Schillinger et al., 2003)

The drawback with these methods is that participants are provided with information on risks, benefits, and alternatives before their concerns have been addressed. Nonetheless, the use of these methods in the consent process has the potential to improve the quality of informed consent for diverse populations, and any of the two methods (teach-back or teach-to-goal) should be considered in the context of clinical research, prior and for the duration of a study.

4.6.4 Techniques for improved communication

There is consistent evidence in the literature to suggest that one of the most effective methods to improve understanding and communicate key information to participants is personal interaction and/or extended discussion with the researcher (Bickmore et al., 2009; Flory & Emanuel, 2004; Nishimura et al., 2013). It has been suggested that verbal interactions

[30] As noted by Schillinger et al. (2003), only by assessing recall and comprehension can the clinician ensure that a key concept has been understood and remembered. Not uncommonly, a patient responds to an initial assessment by demonstrating poor recall, lack of understanding, or health beliefs that may interfere with integration of the concept. The clinician should then repeat, clarify, or tailor subsequent information. To ensure recall and comprehension of this tailored explanation, the clinician should reassess the patient's recall and comprehension until a common understanding has been achieved. Recall and comprehension have been shown to be predictive of subsequent adherence.

facilitate trust and improve comprehension (Tait et al., 2005). As much as it is important for participants to have the opportunity to discuss and voice their concerns before they can reach to some decision, it is also of value to researchers to understand which could be those points of concern about the research study or the process in general. The study by Wade et al. (2009) focused on communication strategies for researchers to elicit participants' views, in order to enable them to understand whether any specific gaps or concerns exist.

The use of open questions elicited views and beliefs rapidly, allowing recruiters to identify which issues participants wished to address. According to Wade et al. (2009), open questions were highly effective but not always sufficient to elicit concerns. It is pointed out that at times recruiters needed to combine open questions with deliberate pauses. It is highlighted in the study that systematic use of open questions and pauses to encourage participants to voice views, concerns and preferences makes leading questions less likely. A further technique used for eliciting participants' views was for the recruiter to cede the floor rapidly where overlapping speech occurred. In those cases where recruiters failed to cede the floor, expression of concerns could be prevented or delayed.

Another method used by Wade et al. (2009) was to adopt a cyclical approach in the process of communication, to explore more in-depth any concerns that emerged in the process. This is based on similar principles to the "teach-back" and "teach-to-goal" methods, however it focuses on addressing concerns rather than providing information on risks, benefits and alternatives to research. It was found that repeated questioning and probing enabled participants to articulate concerns. Recruiters then provided specifically tailored information and elicited further concerns, until, ideally, all had been addressed. It is suggested that focus on what content must be provided in informed consent appointments should broaden. It is crucial for recruiters to explore participants' concerns systematically and establish clearly whether participants are in equipoise.

The study by Yap et al. (2009) developed a model entitled Parent Advisory Group on Informed Consent, as a sequenced approach to improve parental understanding and interactivity during the informed consent process. It emphasised the importance of adherence to a sequence that requires physicians to explain the disease prior to discussion of best available current treatment, and then requires that they offer RCT participation only after they have explained the disease and discussed best available treatment. Yap et al. (2009) concluded that physicians should be trained to conduct effective informed consent conversation prior to presenting the form.

4.6.5 Use of decision aids

The introduction of decision aids in the process is also important to consider in the context of improving informed consent in particular contexts (Gillies et al., 2014). Decision aids inherently focus on the process rather than documents (Brehaut et al., 2010). They help people make specific, deliberative choices among options, use exercises to explicate what issues they find most important, help determine what further information they need, and

provide materials that can be used later for further review and consultation (Brehaut et al., 2010). According to Stacey et al. (2011), there is substantial evidence to suggest that decision aids can positively influence outcomes, such as: improving knowledge, especially when there is clinical equipoise; providing accurate perceptions of outcome probabilities; and aligning preferred outcomes with the choice made.

The decision to participate in clinical research entails participants to make a "preference-sensitive" decision, which basically suggests that decisions about whether to participate depend entirely on how individuals value the potential benefits (e.g. incentives, potential health benefits, altruism) and harms (e.g. side effects, clinic visits) of participation. Decision aids are tools designed to make specific and deliberative choices among various options and possible outcomes presented in relation to the person involved. Decision aids have been shown to improve the quality of "preference-sensitive" decisions, as they reduce uncertainty surrounding decisions, enhance knowledge of key aspects of the decision and outcome probabilities, and improve satisfaction with choices made (Travena et al., 2006).

4.6.6 The case of minority populations

Minority populations suffer from lower levels of health literacy than the general population (George et al., 2013), and such a characteristic makes individuals more vulnerable in relation to the informed consent and decision-making process. Characteristics of minority populations include lack of trust arising from past legacy or mistreatment, or misinformation about the informed consent process and inadequate comprehension of information after the informed consent documents have been signed. According to Quinn et al. (2012), the issue of minority trust in research is an important factor to consider when evaluating ways to improve the process. For instance, a study by Corbie-Smith et al. (2002) revealed a sense of distrust arising from a legacy of mistreatment in the health care system. African Americans were less likely to trust that research would be fully explained to them and more likely to believe that someone like them would be used as a "guinea pig" without his or her consent.

Another study by Ownby et al. (2015) aimed to evaluate the relation of health literacy to understanding orally-presented informed consent information. It was shown that most participants were able to recall some specific information relevant to their participation in a clinical study, with some differences on the basis or demographic characteristics. Race- and ethnicity-specific characteristics were positively correlated with poor performance in recalling specific information, which could further arise from variables such as the level of health literacy and the interaction of health literacy with education. Ownby et al. (2015) conclude that race- and ethnicity-specific differences in the informed consent process could be addressed through tailored interventions for improving health literacy of participants.

A study by Quinn et al. (2012) explored the differences between investigators and community members regarding strategies deemed to be important for increasing understanding and improving the informed consent process. The survey included 347 investigators and 2455 community respondents from minority groups participated in this study. They asked

researchers such questions as "*What methods do you use during the informed consent process?*" "*How do you assess understanding?*" and "*What generally do members of the public know about research terms and the purpose of informed consent?*" They asked community members such questions as "*How would you like to learn about the consent process?*" and "*What strategies do you use to increase understanding, and what methods might be helpful for you to understand the informed consent document?*"

According to the results of the study, most popular and effective methods to implement for better comprehension of the information material were: 1) Going over the consent form one-by-one (78%); 2) Allowing information to be taken home (77%); 3) Having someone read the consent form aloud (65%); 4) Allowing a family member to be present (63%), 5) Allowing more than one meeting (58%) Regarding the presentation and content of informed consent documents, the preferred interventions for community members were: 1) Use of plain language (97%); 2) Use of question and answer format (51%); 3) Use of pictures and illustrations (41%); 4) Use of large print (38%); 5) Include brief summary at the end of each section (19%). Finally, the most effective methods to determine participants' level of understanding during the process were: 1) Ask participants open-ended questions at the end (52%); 2) Have participants sign/initial every page of the ICD (51%); 3) Use teach-back method (38%).

An important discrepancy was noted by Quinn et al. (2012) in preferred methods by community respondents for learning about the study. The methods related to have more than one meeting and talking to someone who is currently participating in the study, are not frequently used or considered by researchers. Multiple meetings and providing access to current participants can be important, although some restrictions are identified, e.g. confidentiality issues, time restraints etc. Group discussion and watching a video were more helpful for increasing comprehension according to community members, while researchers believe that practices should include allowing a family member to be present and reading out loud the informed consent documents. The use of large fonts, pictures/illustrations and providing brief summary to increase understanding, have also been quite popular for community members. According to the authors, it is critical to increase comprehension and satisfaction with the process using methods that research has shown to work, such as one-on-one discussion, multiple meetings, use of plain language, and summaries, and then to make it a standard practice to assess understanding (Quinn et al., 2012).

5. Initiatives for improving the informed consent process

5.1 The Dynamic Consent Initiative

The concept of dynamic consent was developed by Kaye et al. (2015), aiming to offer a novel approach to the consent process. It is defined as "*a new approach for engaging individuals about the use of their personal information. It is also an interactive personalised interface that*

allows participants to engage as much or as little as they choose and to alter their consent choices in real time" (Kaye et al. 2015, p. 142). This participant-centred initiative places patients and research participants at the centre of decision making, providing an interactive IT interface to engage with participants. It is described as "dynamic" because it allows interaction over time; it enables participants to consent to new projects or to alter their consent choices in real time as their circumstances change and to have confidence that these changed choices will take effect.

This initiative was first developed in the field of biobanking, but according to Kaye et al. (2015) it has the potential to be applied more broadly to situations where there are multiple and varied uses of data requiring different kinds of consent over a period of time. Dynamic consent is a secure IT interface for consent and communication that enables participants to view a digital record of what they have consented to, at any time after their initial agreement. Some versions of dynamic consent also have the functionality for people to personalise according to their preferences, which can be changed at any time. Dynamic consent enables two-way, ongoing communication between researchers and research participants. For instance, research participants are able to upload additional health data, or researchers may inform about new research developments.

5.2 The Clinical Trials Transformation Initiative

Further to the identification and analysis of current deficiencies in the informed consent process, the Clinical Trials Transformation Initiative (CTTI) launched the Informed Consent Project. Initial project activities revealed that although an extensive body of literature on informed consent exists, there is little published information examining the observations of experts with long-standing experience with the informed consent process.

The CTTI (www.ctti-clinicaltrials.org) launched a multi-stakeholder Informed Consent Project which sought to define the specific barriers to successful informed consent processes and propose solutions to optimise this process and enhance participant understanding of trial information to inform their decision-making process. Specifically, it was guided by the following objectives (Lentz et al. 2016):

- Understand previous and current efforts to improve the ICP and ICDs, including alternatives to the traditional paper ICD.
- Recognise barriers and identify potential remedies to concisely communicating the required elements of informed consent.
- Propose a more effective process, including informed consent documentation, to ensure study participants' understanding of critical informed consent elements.

The CTTI Project Team comprised a diverse group of stakeholders from across the clinical study enterprise, which developed recommendations for improvement in the IC process toward promoting a research culture that facilitates health-literate informed consent. These recommendations were developed around four key themes:

- Conducting an effective informed consent process
- Enhancing research staff training
- Improving ICDs by developing shorter and simpler documents
- Encouraging exploration of use of electronic consent systems (e-consent)

The CTTI Project Team collected evidence from the literature and conducted a series of expert interviews, including IRB chairs, ethicists, medical device and pharmaceutical senior executives, the US Food and Drug Administration (FDA) and National Institutes of Health (NIH) medical officers/directors, patients and patient advocates, senior clinical-research coordinators, academic medical centre professionals, an electronic consent (e-consent) company executive, and a non-profit organisation executive (Lentz et al., 2016).

The recommendations for each theme were as follows:

Conducting the Informed Consent Process

- The informed consent process should involve an ongoing, interactive conversation between the research participant and the research staff, beginning with initial consideration of study participation and continuing through study completion.
- The informed consent process should be customized to meet the particular needs of individual study participants.
- The person or persons obtaining consent should be skilled in communicating trial - specific information and be responsive to the needs and concerns of individual research participants.
- A discussion tool, not intended as a required regulatory compliance document, could be used as part of the consent process to ensure the following:[31]
    - The specific needs of each study participant are considered,
    - Key elements of the trial are reviewed and addressed, and
    - Interactive techniques are used to facilitate participant understanding of the information imparted.
- Study participants should be provided with available resources to enhance their understanding of clinical trials, including sample questions to ask the investigator so he/she can better engage in a dialogue about the benefits and risks of participation.
- The informed consent document should be viewed as supportive to the consenting process, rather than the primary focus.

Training of research stuff

- Research staff obtaining consent should be trained to do so.

[31] The CTTI recommendations document provides a tool for documenting the informed consent process. This tool helps to ensure: a) the specific needs of each study participant are considered, b) critical elements of the study are reviewed and addressed, and c) interactive techniques are used to facilitate study participants' understanding. For more information, and the full version of the checklist, see Appendix I <https://www.ctti-clinicaltrials.org/files/ctti-informedconsent-recs.pdf>

- Training programs should be determined by individual research sites and tailored to local and organisational needs. A uniform training program is not required, and programs should not be nationally driven or sponsor-specific.
- For research staff designated to obtain consent, an informed consent training program should aim to improve their knowledge and communication skills, including best practices to impart trial-specific information while remaining sensitive to participants' needs.
- An ideal training program should include the following:[32]
    - Didactic information, which may be part of other general clinical research training.
    - Interactive opportunities to practice or get feedback on communication techniques, and
    - Continuing education as needed.
- Professional organizations and/or NIH should develop comprehensive training programs research sites can choose to use as, or as a part of, their organizational informed consent training program.
- Patients should be included in the development and/or implementation of the training program. Resources for meaningful patient engagement should be utilized.
- The benefits and effectiveness of training should be assessed.

Informed Consent Document Template

- A tiered approach should be used in the informed consent document.
    - The first tier of the informed consent document should contain only the elements of informed consent required by federal regulation.
    - The second tier should contain additional information, in chapter format, on a range of study-related issues for each study participant to review as deemed necessary. This detailed reference section would provide an elaboration of the information in the informed consent document and be made available to study participants who wish to review it.
    - A third tier consisting of a 1-2 pages introduction or a summary of the study may be valuable for more complex studies.
- Draft informed consent documents should be evaluated with the following methods:
    - Standardised health literacy/plain language assessments
    - Reading level assessments
    - Usability testing with patients similar to those who would be eligible for the study
- A standard language library should be developed for text that is not specific to the study, and is universally accessible to study sponsors.

E-consent

[32] The CTTI recommendations document provides potential criteria by which to evaluate training programs. For more information see Appendix II : <https://www.ctti-clinicaltrials.org/files/ctti-informedconsent-recs.pdf>

- E-consent facilitates the use of the recommended tiered informed consent document.
- Research sponsors and investigative sites should continue to explore the use of e-consent and share best practices and lessons learned. Interventional trials of e-consent documents should be conducted to evaluate the effects on study feasibility and participant comprehension, decision-making, and satisfaction.

6. Conclusion

The present report has been prepared in the scope of WP1: A multi-layered approach to informed consent. This report is divided into three main parts, namely: a) a philosophical discussion about the notion of consent and associated concepts; b) an analysis of the conceptual frameworks built around informed consent as represented in standards and requirements of international guidelines; c) a comprehensive review of the scientific literature to identify methods and strategies for improving informed consent at different stages of clinical research studies, from preparation to communication and evaluation.

In the philosophical discussion in Section 2 we argued for a "thin" conception of consent, which is to say that, in contrast to other positions from the literature, we do not insist upon a conception of consent as "a core moral notion," nor upon its necessarily having a legitimising normative force in any strongly ethical sense (which is not to say it has no normative force). In the context of informed consent in research, we argued that consent processes have instrumental value as effective means of securing core ethical goals. As the reviews of consent in the history of ideas in the Western tradition and in the Nuremburg code revealed, autonomy has frequently been taken as the key ethical value justifying consent processes. However we pointed out that there is nothing to rule out informed consent being a protection of a number of rights and interests of potential research subjects, including the right to autonomy, to fair treatment, and a number of others. This, we observed, sat well with the account of normative agency proposed by Griffin (2008: 149).

The notion of informed consent was conceived as the means to ensure the ethical conduct of research, presenting a paradigm shift from a deeply-rooted paternalistic model, often based in persuasive authority relations, especially in the context of clinical research and experimentation with human participants. Key international guidelines for clinical research, such as the Declaration of Helsinki and the CIOMS Guidelines have been developed with the aim to provide ethical and regulatory standards for the conduct of research. These international guidelines put more focus on core elements and information to be disclosed to potential participants via the informed consent documents, and over the course of time this resulted in having excessively lengthy documents and complex information presented, also in an effort to ensure better liability protection from the side of researchers.

There is a considerable body of literature which looks into different interventions that could be implemented at the level of informed consent document, on the basis of how information should be presented, rather than what needs to be presented. Empirical evidence to date (Flory & Emanuel; Nishimura et al, 2013) indicates that extended discussion interventions may be more consistently effective than approaches using multimedia or enhanced forms at improving understanding. In general terms, the improvement of informed consent as a process requires a combination of written, verbal, and multimedia formats, as well as the employment of various communication techniques. The most promising avenue for improving informed consent would be to consider this as a process, which can be tailored to be

consistent with research subjects' values, interests and preferences. This, we note, is in accordance with various findings from the philosophical discussion in Section 2.

References

Ahalt, C., Sudore, R., Bolano, M., et al. (2017). "Teach-to-Goal" to better assess informed consent comprehension among incarcerated clinical research participants. *Journal of Ethics*, *19*(9), 862-872.

Albala, I., Doyle, M. & Appelbaum, P. S. (2010). The evolution of consent forms for research: A quarter century of changes. *IRB*, *32*(3), 7-11.

Allmark, P. & Mason, S. (2006). Improving the quality of consent to randomised controlled trials by using continuous consent and clinician training in the consent process. *Journal of Medical Ethics*, *32*(8), 439-443.

Austin, J.L. (1962). How to do things with words, 2nd Edition, J.O. Urmson & M. Sbisá (Eds). Cambridge, MA: Harvard University Press.

Beauchamp, T.L. (2010). Autonomy and consent. In F.G. Miller & A. Wertheimer (Eds.) *The Ethics of Consent: Theory and Practice* (pp. 55–78). Oxford: Oxford University Press.

Beauchamp, T. L. & Childress, J. F. (1994). *Principles of biomedical ethics* (4th ed). New York: Oxford University Press.

Bergenmar, M., Johansson, H., Wilking, N., et al. (2014). Audio-recorded information to patients considering participation in cancer clinical trials – a randomized study. *Acta Oncologica*, *53*, 1197-1204.

Berger, O., Gronberg, B. H., Sand, K., Kaasa, S. & Loge, J. H. (2009). The length of consent documents in oncological trials is doubled in twenty years. *Annals of Oncology*, *20*(2), 379-385.

Bhutta, Z. A. (2004). Beyond informed consent. *Bulletin of the World Health Organization*, *82*(10), 771-777.

Bickmore, T. W., Pfeiffer, L. M. & Paasche-Orlow, M. K. (2009). Using computer agents to explain medical documents to patient with low health literacy. *Patient Education and Counseling*, *75*(3), 315-320.

Bjorn, E., Rossel, R., & Holm, S. (1999). Can the written information to research subjects be improved? *Journal of Medical Ethics*, *25*, 263-267.

Brehaut, J. C., Carroll, K., Elwyn, G. et al. (2015). Elements of informed consent and decision quality were poorly correlated in informed consent documents. *Journal of Clinical Epidemiology*, *68*, 1472-1480.

Brehaut, J. C., Fergusson, D. A., Kimmelman, J. et al. (2010). Using decision aids may improve informed consent for research. *Contemporary Clinical Trials*, *31*, 218-220.

Brehaut, J. C., Saginur, R. & Elwyn, G. (2009). Informed consent documentation necessary but not sufficient. *Contemporary Clinical Trials*, *30*, 388-389.

Butters, R., Sugarman, J. & Kaplan, L. (2000). Semantic and pragmatic variability in medical research terms: Implications for obtaining informed consent. *American Speech*, *75*(2), 149-168.

Calderón, J. L., Singer, G., Heslin, K., et al. (2007). Animation as a venue for enhancing health literacy: Implications for medical education. *Annals of Behavioral Sciences and Medical Education*, *13*(2), 87-91.

Corbie-Smith, G., Thomas, S. B., Williams, M. V., et al. (1999). Attitudes and beliefs of African Americans toward participation in medical research. *Journal of General Internal Medicine*, *14*(9), 537-546.

Cummings, S. R. & Rowbotham, M. C. (2017). Electronic informed consent and internet-based trials. *The New England Journal of Medicine*, *376*(9), 859-861.

Darwall, S. (2001). Normativity. In *The Routledge Encyclopedia of Philosophy*. Taylor and Francis. Retrieved October 27, 2017, from https://www.rep.routledge.com/articles/thematic/normativity/v-1. doi:10.4324/9780415249126-L135-1

Davis, T. C., Holcombe, R. F., Berkel, H. J. et al. (1998). Informed consent for clinical trials: A comparative study of standard versus simplified forms. *Journal of National Cancer Institute*, *90*, 668-674.

Dellson, P., Nilbert, M. & Carlsson, C. (2016). Patient representatives' views on patient information in clinical cancer trials. *BMC Health Services Research*, 16:36.

Directive on privacy and electronic communications 2002 (European Union).

Donovan-Kicken, E., Mackert, M., Guinn, T., et al. (2013). Sources of patient uncertainty when reviewing medical disclosure and consent documentation. *Patient Education and Counseling*, *90*, 254-260.

Donovan-Kicken, E., Tollison, A. C., & Goins, E. S. (2012). The nature of communication work during cancer: Advancing the theory of illness trajectories. *Health Communication*, *27*(7), 641-652.

Dresden, G. M. & Levitt, M. A. (2001). Modifying a standard industry clinical trial consent form improves patient information retention as part of the informed consent process. *Academic Emergency Medicine*, *8*(3), 246-252.

Emanuel, E. J., Wendler, D. & Grady, C. (2000). What makes clinical research ethical? *Journal of the American Medical Association*, *283*(20), 2701-2711.

European Commission. (2016). *Information providers guide: the EU Internet handbook – cookies* (website). Retrieved August 9, 2017, from http://ec.europa.eu/ipg/basics/legal/cookies/index_en.htm

Faden, R.R., & Beauchamp, T.L. (1986). *A history and theory of informed consent*. New York: Oxford University Press.

Falagas, M. E., Korbila, I. P. & Giannopoulou, K. P. (2009). Informed consent: How much and what do patients understand? *The American Journal of Surgery*, *198*, 420-435.

George, S., Moran, E., Duran, N., et al. (2013). Using animation as an information tool to advance health research literacy among minority participants. *AMIA Annual Symposium Proceedings*, *2013*, 475-484.

Gillies, K., Huang, W., Skea, Z., et al. (2014). Patient information leaflets (PILs) for UK randomised controlled trials: A feasibility study exploring whether they contain information to support decision making about trial participation. *Trials*, *15*:62.

Grady, C. R. N. (2017). The changing face of informed consent. *The New England Journal of Medicine*, *376*(9), 856-859.

Griffin, J. (2008). *On Human Rights*. Oxford: Oxford University Press.

Grice, H.P. (1989). *Studies in the ways of words*. Cambridge, MA: Harvard University Press.

Hawley, S., Zikmund-Fisher, B., Ubel, P. et al. (2008). The impact of the format of graphical presentation on health-related knowledge and treatment choices. *Patient Education and Counseling*, *73*, 448-455.

Hill, Jr., T.E. (1980). Humanity as an end in itself. *Ethics*, *91*, 84–99.

Hobbes, T. (1953[1651]). *Leviathan*. London: J.M. Dent & Sons.

Hochhauser, M. (2003). Concepts, categories, and value judgments in informed consent forms. *IRB*, *25*(5), 7-10.

Hoffner, B., Bauer-Wu, S., Hitchcock-Bryan, S., et al. (2012). "Entering a clinical trial: Is it right for you?" – A randomised study of the clinical trials video and its impact on the informed consent process. *Cancer*, *118*(7), 1877-1883.

Hurd, H.M. (1996). The moral magic of consent. *Legal Theory, 2*, 121–146.

Jefford, M. & Moore, R. (2008) Improvement of informed consent and the quality of consent documents. *The Lancet Oncology*, *9*, 485-493.

Johnston, D. (2010). A history of consent in Western thought. In F.G. Miller & A. Wertheimer (Eds.) *The Ethics of Consent: Theory and Practice* (pp. 25–54). Oxford: Oxford University Press.

Karunaratne, A. S., Korenman, S. G., Thomas, S. L., et al. (2010). Improving communication when seeking informed consent: A randomised controlled study of a computer-based method

for proving information to prospective clinical trial participants. *The Medical Journal of Australia*, *192*(7), 388-392.

Kass, N., Taylor, H., Ali, J., et al. (2015). A pilot study of simple interventions to improve informed consent in clinical research: Feasibility, approach and results. *Clinical Trials*, *12*(1), 54-66.

Kaye, J., Whitley, E. A., Lund, D., et al. (2015). Dynamic consent: A patient interface for twenty-first century research networks. *European Journal of Human Genetics*, *23*, 141-146.

Kim, E. J. & Kim, S. H. (2015). Simplification of improves understanding of informed consent information in clinical trials regardless of health literacy level. *Clinical Trials*, *12*(3), 232-236.

Kleinig, J. (2010). The nature of consent. In F.G. Miller & A. Wertheimer (Eds.) *The Ethics of Consent: Theory and Practice* (pp. 3–24). Oxford: Oxford University Press.

Koyfman, S. A., Agre, P., Carlisle, R., et al. (2013). Consent form heterogeneity in cancer trials: The cooperative group and institutional review board gap. *Journal of the National Cancer Institute*, *105*, 947-953.

Lakes, K. D., Vaughan, E., Jones, M., et al. (2012). Diverse perceptions of the informed consent process: Implications for the recruitment and participation of diverse communities in the National Children's Study. *American Journal of Community Psychology*, *49*, 215-232.

Lentz, J., Kennett, M., Perlmutter, J. et al. (2016). Paving the way to a more effective informed consent process: Recommendations from the Clinical Trials Transformation Initiative. *Contemporary Clinical Trials*, *49*, 65-69.

Lloyd, C. E., Johnson, M. R. D., Mughal, S., et al. (2008). Securing recruitment and obtaining informed consent in minority ethnic groups in the UK. *BMC Health Services Research*, *8*(68), 1-9.

Locke, J. (1993[1690]). *An essay concerning human understanding*. London: Everyman.

Lorell, B. H., Mikita, J. S. Anderson, A. (2015). Informed consent in clinical research: Consensus recommendations for reform identified by an expert interview panel. *Clinical Trials*, *12*(6), 692-695.

Lorenzen, B., Melby, C. E. & Earles. B (2008). Using principles of health literacy to enhance the informed consent process. *AORN Journal*, *88*, 23-29.

Maclean, A. (2013). *Autonomy, informed consent and medical law: a relational challenge*. Cambridge: Cambridge University Press.

Manson, N.C., & O'Neill, O. (2007). *Rethinking informed consent in bioethics*. Cambridge: Cambridge University Press.

Matiasek, J. & Wynia. M. (2008). Reconceptualizing the informed consent process at eight innovative hospitals. *Joint Commission Journal on Quality and Patient Safety*, *34*(3), 127-137.

McKay, T. & Nelson, M. (2014). Propositional attitude reports. In E.N. Zalta (Ed.) *The Stanford Encyclopedia of Philosophy (Spring 2014 Edition).* Retrieved October 18, 2017, from, https://plato.stanford.edu/archives/spr2014/entries/prop-attitude-reports/

Meade, C. D. (1999). Improving understanding of the informed consent process and document. *Seminars in Oncology Nursing*, *15*(2), 124-137.

Meneguin, S. & Ayres, J. A. (2014). Perception of the informed consent form by participants in clinical trials. *Investigación y Educación en Enfermería*, *32*(1), 95-102.

Mill, J.S. (2006[1859]). *On liberty and the subjugation of women*. London: Penguin.

Miller, F.G. (2010). Consent to clinical research. In F.G. Miller & A. Wertheimer (Eds.) *The Ethics of Consent: Theory and Practice* (pp. 375–404). Oxford: Oxford University Press.

Miller, F.G., & Wertheimer, A. (2010a). Preface to a theory of consent transactions: beyond valid consent. In F.G. Miller & A. Wertheimer (Eds.) *The Ethics of Consent: Theory and Practice* (pp. 79–105). Oxford: Oxford University Press

Miller, F.G., & Wertheimer, A. (2010b). *The ethics of consent: theory and practice*. Oxford: Oxford University Press.

Morris, M. (2007. *An introduction to the philosophy of language*. Cambridge: Cambridge University Press.

Nelson, D. L., Reed, U. S. & Walling, J. R. (1976). Pictorial superiority effect. *Journal of Experimental Psychology*, *2*(5): 523-528.

Nishimura, A., Carey, J., Erwin, P. J., et al. (2013). Improving understanding in the research informed consent process: A systematic review of 54 interventions tested in randomised controlled trials. *BMC Medical Ethics*, 14:28.

The Nuremberg Code. (1947). Retrieved July 17, 2017, from https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial/nuremberg-code

Nystrand, M. (1986). *The structure of written communication: Studies in reciprocity between writers and readers*. Orlando: Academic.

O'Neill, O. (2002). *Autonomy and trust in bioethics*. Cambridge: Cambridge University Press.

O'Neill, O. (2003). Some limits of informed consent. *Journal of Medical Ethics, 29*, 4–7.

O'Neill, O. (2004). Informed consent and public health. *Philosophical Transactions: Biological Sciences, 359*, 1133–6.

Ownby, R. L., Acevedo, A., Goodman, K., et al. (2015). Health literacy predicts participant understanding of orally-presented informed consent information. *Clinical Research and Trials*, *1*(1), 15-19.

Paasche-Orlow, M. K., Taylor, H. A. & Brancati. F. I. (2003). Readability standards for informed-consent forms as compared with actual readability. *New England Journal of Medicine*, *348*, 721-726.

Paasche-Orlow, M. K., Brancati, F. L., Taylor, H. A., et al. (2013). Readability of informed consent templates: A second look. *IRB: Ethics & Human Research*, *35*(4), 12-19.

Padhy, B. M., Gupta, P. & Gupta, Y. K. (2011). Analysis of the compliance of informed consent documents with good clinical practice guideline. *Contemporary Clinical Trials*, *32*, 662-666.

Palmer, B. W., Lanouette, N. M. & Doyle, W. J. (2012). Effectiveness of multimedia aids to enhance comprehension of research consent information: A systematic review. *IRB*, *31*, 1-15.

Paris, A., Deygas, B., Cornu, C. et al. (2015). Improved informed consent documents for biomedical research do not increase patients' understanding but reduce enrolment: A study in real settings. *British Journal of Clinical Pharmacology*, *80*, 1010-1020.

Plato. (1992[380 BC]). *The republic* (G.M.A. Grube and C.D.C. Reeve Trans.). Indianapolis: Hackett.

Quinn, S. C., Garza, M. A., Butler, J., et al. (2012). Improving informed consent with minority participants: Results from researcher and community surveys. *Journal of Empirical Research on Human Research Ethics*, *7*(5), 44-55.

Rapist who agreed to use condom gets 40 years. (1993). *The New York Times, May 15, 1993.* Retrieved from http://www.nytimes.com/1993/05/15/us/rapist-who-agreed-to-use-condom-gets-40-years.html

Rosoff, A. J. (1999). Informed consent in the electronic age. *American Journal of Law and Medicine, 25*, 367-386.

Rousseau, J-J. (1987[1762]). On the social contract. In J-J. Rousseau, *The Basic Political Writings* (D.A. Cress Trans.). Indianapolis: Hackett.

Rowbotham, M. C., Astin, J., Greene, K. & Cummings, S. R. (2013). Interactive informed consent: Randomized comparison with paper consents. *PLoS ONE*, *8*(3): e58603.

Ryan, R., Prictor, M., McLaughlin, K. J. & Hill, S. (2008). Audio-visual presentation of information for informed consent for participation in clinical trials. *Cochrane Database Systematic Review*, 23:CD003717.

Sand, K., Eik-Nes N. L. & Loge, J. H. (2012). Readability of informed consent documents (1987-2007) for clinical trials: A linguistic analysis. *Journal of Empirical Research on Human Research Ethics*, *7*(4), 67-78.

Schenker, Y. & Meisel, A. (2011). Informed consent in clinical care: Practical considerations in the effort to achieve ethical goals. *Journal of the American Medical Association*, *305*, 1130-1131.

Schillinger, D., Piette, J., Grumbach, K., et al. (2003). Closing the loop: Physician communication with diabetic patients who have low health literacy. *Archive of Internal Medicine*, *163*, 83-90.

Schlosser, M. (2015). Agency. In E.N. Zalta (Ed.) *The Stanford Encyclopedia of Philosophy (Fall 2015 Edition).* Retrieved October 27, 2017, from, https://plato.stanford.edu/archives/fall2015/entries/agency/

Sharp, S. M. (2001). Improving the process of informed consent. *Applied Clinical Research*, *10*, 4-82.

Shuster, E. (1997). Fifty years later: The significance of the Nuremberg Code. *The New England Journal of Medicine*, *Special Article*, 1436-1440.

Sims, J. (2010). A brief review of the Belmont Report. *Dimensions of Critical Care Nursing*, *29*(4), 173-4.

Sonne, S. C., Andrews, J. O., Gentilin, S. M., et al. (2013). Development and pilot-testing of a video-assisted informed consent process. *Contemporary Clinical Trials*, 36(1), 25-31.

Stacey, D., Bennett, C. L., Barry, M. J., et al. (2011). Decision aids for people facing health treatment or screening decisions. *Cochrane Database of Systematic Reviews*, *4*:CD001431.

Stunkel, L., Benson, M., McLellan, L., et al. (2010). Comprehension and informed consent: Assessing the effect of a short consent form. *IRB*, *32*(4), 1-9.

Sudore, R. L., Landefeld, S., Williams, B. A., et al. (2006). Use of a modified informed consent process among vulnerable patients. *Journal of General Internal Medicine*, *21*, 867-873.

Sugarman, J., Lavori, P. W., Boeger, M., et al. (2005). Evaluating the quality of informed consent. *Clinical Trials*, *2*, 34-41.

Synnot, A., Ryan, R., Prictor, M. et al. (2014). Audio-visual presentation of information for informed consent for participation in clinical trials. *Cochrane Database of Systematic Reviews*, 5:CD003717.

Tait, A. R. & Voepel-Lewis, T. (2015). Digital multimedia: A new approach for informed consent? *Journal of American Medical Association*, *313*, 463-464.

Tait, A. R., Voepel-Lewis, T., Malviya, S., et al. (2005). Improving the readability and processability of a pediatric informed consent document. *Archives of Pediatrics and Adolescent Medicine*, *159*, 347-352.

Tait, A. R., Voepel-Lewis, T., Zikmund-Fisher, B. J. & Fagerlin, A. (2010). The effect of format on parents' understanding of the risks and benefits of clinical research: A comparison between text, tables and graphics. *Journal of Health Communication*, *15*(5), 487-501.

Tamariz, L., Palacio, A., Robert, M. & Marcus, E.N. (2012). Improving the informed consent process for research subjects with low literacy: A systematic review. *Journal of General Internal Medicine*, *28*(1), 121-126.

Tourangeau, R. (1984). Cognitive science and survey methods: A cognitive perspective. In T. Jabine, M. Straf, J. Tanur, & R. Tourangeau (Eds.), *Cognitive aspects of survey design: Building a bridge between disciplines* (pp. 73-100). Washington, DC: National Academy Press.

Travena, L., Davey, H. M., Barratt, A., et al. (2006). A systematic review on communicating with patients about evidence. *Journal of Evaluation in Clinical Practice*, *12*, 13-23.

Vučemilo, L. & Borovečki, A. (2015). Readability and content assessment of informed consent forms for medical procedures in Croatia. *PLoS ONE*, *10*(9):e0138017.

Wade, J., Donovan, J. L., Lane, J. A., et al. (2009). It's not just what you say, it's also how you say it: Opening the 'black box' of informed consent appointments in randomised controlled trials. *Social Science & Medicine*, *68*, 2018-2028.

Wen, G. Liu, X. Huang, L. et al. (2016). Readability and content assessment of informed consent forms for phase II-IV clinical trials in China. *PLoS ONE*, *11*(10):e0164251.

Wendler, D. & Rackoff, J. (2007). Consent for continuing research participation. *IRB*, *24*(3), 1-6.

Westen, P. (2013). *The logic of consent: the diversity and deceptiveness of consent as a defence to criminal conduct*. Aldershot: Ashgate.

Willis, G. (2006). Cognitive interviewing as a tool for improving the informed consent process. *Journal of Empirical Research on Human Research Ethics*, 9-24.

World Medical Association (WMA). (2013). *The WMA Declaration of Helsinki.* Retrieved July 19, 2017 from https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Yap, T. Y., Yamokoski, A., Noll, R. et al. (2009). A physician-directed intervention: Teaching and measuring better informed consent. *Academic Medicine*, *84*(8), 1036-1042.

Annex I _ EU-funded projects related to informed consent

EU FUNDED PROJECTS RELATED TO INFORMED CONSENT

Table of contents

SIENNA

Project ID: 741716
Funded under:
H2020-EU.5.c. - Integrate society in science and innovation issues, policies and activities in order to integrate citizens' interests and values and to increase the quality, relevance, social acceptability and sustainability of research and innovation outcomes in various fields of activity from social innovation to areas such as biotechnology and nanotechnology
H2020-EU.5.f. - Develop the governance for the advancement of responsible research and innovation by all stakeholders, which is sensitive to society needs and demands and promote an ethics framework for research and innovation
H2020-EU.5.g. - Take due and proportional precautions in research and innovation activities by anticipating and assessing potential environmental, health and safety impacts

Stakeholder-informed ethics for new technologies with high socio-economic and human rights impact

From 2017-10-01 **to** 2021-03-31, Grant Agreement signed

Project details

Total cost:

EUR 3 996 787,5

EU contribution:

EUR 3 996 787,5

Coordinated in:

Netherlands

Topic(s):

SwafS-18-2016 - The Ethics of technologies with high socio-economic impact and Human Rights relevance

Funding scheme:

CSA - Coordination and support action

Objective

SIENNA is a three and a half year project with 11 core partners and 2 associate partners, focussing on ethical and human rights challenges posed by human genomics, human enhancement and human-machine interaction technologies such as robots and smart devices. While these technologies offer significant benefits to individuals and society, they also present significant ethical challenges, e.g., in relation to human autonomy, equality, personal liberty, privacy, and accountability. In collaboration with a variety of stakeholders, SIENNA will identify and assess the ethical and socio-economic issues, public opinions, legal regulation and human rights implications of each technology. It will produce a framework for each of the three technologies that will form the basis for the development of research ethics protocols, professional ethical codes, and better ethical and legal frameworks. Before developing their recommendations, the partners will gather ethical views of experts and citizens towards the three technologies in four ways: (1) a major survey of citizens in 11 countries within and outside the EU; (2) panels of citizens in five countries; (3) interviews with experts and stakeholders; (4) workshops with stakeholders including scientists, ethicists, research ethics committees, professional organisations, civil society organisations, industry and policy makers. SIENNA will boost the EU's leadership in developing ethical standards and support its vision of Responsible Research and Innovation (RRI) as a means to foster the design of inclusive research and innovation. The project will improve knowledge of the ethical, human rights and socio-economic impacts of the three technologies, while supporting ethical and responsible decision making by research ethics committees, scientific researchers and policy makers in the three areas. SIENNA will also create added value by generalising its methods for use in other emerging technological domains.

Coordinator

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Netherlands
EU contribution: EUR 1 918 937,5

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TRILATERAL RESEARCH LTD
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W14 8TH LONDON
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EU contribution: EUR 585 937,5

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Sweden

Sweden
EU contribution: EUR 806 555

HELSINSKA FUNDACJA PRAW CZLOWIEKA
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EU contribution: EUR 155 812,5

EUROPEAN NETWORK OF RESEARCH ETHICS COMMITTEES (EUREC) EV
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EU contribution: EUR 201 500

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EU contribution: EUR 38 497,5

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China
EU contribution: EUR 24 437,5

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EU contribution: EUR 58 900

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South Africa

EU contribution: EUR 49 072,5

Last updated on 2017-06-10
Retrieved on 2017-08-07

Permalink: http://cordis.europa.eu/project/rcn/210254_en.html

EnTIRE

Project ID: 741782
Funded under:
H2020-EU.5.f. - Develop the governance for the advancement of responsible research and innovation by all stakeholders, which is sensitive to society needs and demands and promote an ethics framework for research and innovation

Mapping Normative Frameworks for EThics and Integrity of REsearch

From 2017-05-01 **to** 2021-04-30, ongoing project

Project details

Total cost:	**Topic(s):**
EUR 3 770 000	SwafS-16-2016 - Mapping the Ethics and Research Integrity Normative Framework
EU contribution:	**Funding scheme:**
EUR 3 770 000	CSA - Coordination and support action
Coordinated in:	
Netherlands	

Objective

Our aim is to create a platform that makes the normative framework governing Research Ethics and Research Integrity (RE+RI) easily accessible, supports application in research and evaluation, and involves all stakeholders in a participatory way, thus achieving sustainability. The platform will foster uptake of ethical standards and responsible conduct of research, and ultimately support research excellence and strengthen society's confidence in research and its findings.

This project has three unique features:

1. Stakeholder participation and community engagement
The first unique feature is the iterative, 'bottom up' approach, making explicit normative experiences of local stakeholders and principles embedded in local standards, rules and practices, and enabling a structuring of data that fits research and evaluation practice, providing useful, accessible information for local users.

2. Focus on (diversity of) RE+RI practices
The second unique feature is acknowledging the diversity of practices within and between countries and disciplines. Through normative analysis, differences wil be made explicit and open for comparison and deliberation. By using various methods of case analysis, prominent RE+RI cases from practice will be made accessible and scenarios will be developed. This will result in a structuring of data, based on their relevance for actual use by researchers.

3. Interactive self-sustainable Wiki-platform
The third unique feature is the development of an online platform that is dynamic, customer-tailored, up-to-date and self-sustainable. Based upon the MediaWiki approach, committed to open source and open data, the platform steers a user through its content based on what he seeks and what he needs to know. The platform will be adapted and further developed using the latest novelties in knowledge engineering (data mining). It will be owned by the RE+RI community, which will ensure that it is up-to-date and sustainable.

Coordinator

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DE BOELELAAN 1117
1081 HV AMSTERDAM
Netherlands

Netherlands

EU contribution: EUR 1 161 000

Participants

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92521 SCHWARZENFELD
Germany

Germany

EU contribution: EUR 485 000

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Belgium

Belgium

EU contribution: EUR 579 000

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Croatia

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9 DUBLIN
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Ireland

EU contribution: EUR 486 000

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EU contribution: EUR 151 000

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EU contribution: EUR 125 000

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EU contribution: EUR 153 000

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EU contribution: EUR 104 000

EUROPEAN NETWORK OF RESEARCH ETHICS COMMITTEES (EUREC) EV
BONNER TALWEG 57
53111 BONN
Germany

Germany

EU contribution: EUR 80 000

Last updated on 2017-05-04

ORION

Project ID: 741527
Funded under:
H2020-EU.5.f. - Develop the governance for the advancement of responsible research and innovation by all stakeholders, which is sensitive to society needs and demands and promote an ethics framework for research and innovation

Open Responsible research and Innovation to further Outstanding kNowledge.

From 2017-05-01 **to** 2021-04-30, ongoing project

Project details

Total cost:	**Topic(s):**
EUR 3 157 301,25	SwafS-04-2016 - Opening Research Organisations in the European Research Area
EU contribution:	**Funding scheme:**
EUR 3 157 301,25	CSA - Coordination and support action
Coordinated in:	
Spain	

Objective

The ORION project focuses on triggering evidence-based institutional, cultural and behavioural changes in Research Funding and Performing Organizations (RFPOs), targeting researchers, management staff and high-level leadership. Our long term vision is to “embed” Open Science and Responsible Research and Innovation (RRI) principles in RPFOs’ policies, practices and processes to organise and do research. Since science is about creativity and collaboration, we will extend further collaboration in research by engaging in co-creation experiments with multiple stakeholders. We will try out different “open-experiments” in three key challenge areas: 1) Opening up the research engine – making RFPOs more permeable to receiving input from numerous, distinct stakeholders; 2) Identifying risks and opportunities presented by disruptive technologies; 3) Running multi-stakeholder projects based on citizen science. After an initial assessment and benchmarking exercise, we will use our three challenges as case studies to explore different co-creation methods with multiple stakeholders, and spark dialogue between unusual combinations of actors (e.g. funders and the public, or researchers, industry and the public). We will apply the RRI principles on the scientific process and governance, identify drivers and barriers, interests and values, and eventually produce “prototypes” for current and future societal challenges. Toward raising knowledge on RRI in practice and enriching the current training, we will generate innovative training programmes and modules based on the peer-to-peer learning approach, targeting young researchers and professionals at funding agencies. The consortium, which involves RPFOs from different countries, representatives of RRI stakeholders and experts in social sciences, will move forward to achieve and embed Open Science.

Coordinator

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EU contribution: EUR 853 750

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EU contribution: EUR 176 875

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EU contribution: EUR 55 750

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Permalink: http://cordis.europa.eu/project/rcn/210249_en.html

NewHoRRIzon

Project ID: 741402
Funded under:
H2020-EU.5.f. - Develop the governance for the advancement of responsible research and innovation by all stakeholders, which is sensitive to society needs and demands and promote an ethics framework for research and innovation

Excellence in science and innovation for Europe by adopting the concept of Responsible Research and Innovation

From 2017-05-01 **to** 2021-04-30, ongoing project

Project details

Total cost:

EUR 6 799 943

EU contribution:

EUR 6 799 943

Coordinated in:

Austria

Topic(s):

SwafS-09-2016 - Moving from constraints to openings, from red lines to new frames in Horizon 2020

Funding scheme:

CSA - Coordination and support action

Objective

The Project “Excellence in science and innovation for Europe by adopting the concept of Responsible Research and Innovation (NewHoRRIzon)” sets out to promote the acceptance of RRI in Horizon 2020 (H2020) and beyond. It will work out the conceptual and operational basis to fully integrate RRI into European and national research and innovation (R&I) practice and funding. In order to accomplish this goal, NewHoRRIzon will establish altogether 18 Social Labs that cover all sections of H2020. Together with a wide-ranging group of R&I stakeholders, in these Social Labs, NewHoRRIzon will co-create tailor-made pilot actions that will stimulate an increased use and acceptance of RRI across H2020 and each of its parts. These pilot actions will address a variety of R&I actors such as academia, business, non-university research institutes, research funding organisations, policy-makers on European, Member State and global level, civil society organisations (CSOs) and the general and specific public(s) as they arise from technological controversies. Ultimately, the pilot actions to be developed and tested in the Social Labs will contribute to R&I projects that fully recognise the significance of RRI. NewHoRRIzon will stimulate learning about how to accomplish RRI in H2020 and beyond in its Social Labs, in two cross-sectional workshops and two transdisciplinary conferences. It will conceptualise and operationalise a Society Readiness Level (SRL) for R&I that focuses on the alignment between the processes and products of R&I on the one hand, and broader societal demands and expectations on the other. Finally, NewHoRRIzon will use a variety of target-group specific strategies to disseminate best practises to promote acceptance of RRI across H2020 and generate long-term impact. For that it will use existing spaces and networks as well as create new ones.

Coordinator

INSTITUT FUER HOEHERE STUDIEN - INSTITUTE FOR ADVANCED STUDIES
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EU contribution: EUR 685 625

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EU contribution: EUR 171 090

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EU contribution: EUR 70 062,5

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EU contribution: EUR 30 581,25

Last updated on 2017-04-21
Retrieved on 2017-08-07

Permalink: http://cordis.europa.eu/project/rcn/210048_en.html

InSPIRES

Project ID: 741677
Funded under:
H2020-EU.5.c. - Integrate society in science and innovation issues, policies and activities in order to integrate citizens' interests and values and to increase the quality, relevance, social acceptability and sustainability of research and innovation outcomes in various fields of activity from social innovation to areas such as biotechnology and nanotechnology
H2020-EU.5.f. - Develop the governance for the advancement of responsible research and innovation by all stakeholders, which is sensitive to society needs and demands and promote an ethics framework for research and innovation

Ingenious Science shops to promote Participatory Innovation, Research and Equity in Science.

From 2017-04-01 **to** 2021-03-31, ongoing project

Project details

Total cost:	**Topic(s):**
EUR 2 995 606,25	SwafS-01-2016 - Participatory research and innovation via Science Shops
EU contribution:	**Funding scheme:**
EUR 2 995 606,25	RIA - Research and Innovation action
Coordinated in:	
Spain	

Objective

InSPIRES brings together practitioners and experts from across and beyond Europe to co-design, jointly pilot, implement and roll out innovative models for Science Shops (SS). The InSPIRES models integrate Responsible Research and Innovation, Open Science and Impact Evaluation as part of their DNA in order to open the research process up in a more strategic way to civil society and other stakeholders. The inputs from systematic impact evaluation studies will be continuously integrated in order to make InSPIRES SS 2.0 models more accurate and responsive to civil society needs and concerns. Concentrating most of its efforts on Research & Innovation in the health sector, with a strong focus on the environmental and social determinants, and giving special attention to gender parity and vulnerable groups (women, the elderly, adolescents, migrants and refugees), InSPIRES brings Science Cafés and other public engagement initiatives into its models together with a “glocal” international focus, for more inclusive, context relevant and culturally adapted community-based participatory research and innovation. Building on a comprehensive communication plan, with a strong effort dedicated to the development and implementation of a sustainability strategy, InSPIRES outcomes will: a) give evidence and support political bodies and decision-makers, in order to propose changes in local, regional, national and international policies; b) nurture the debate about the place and role of society in science, encouraging the systematic and ethical involvement of civil society actors and their societal concerns in the research and innovation processes, and c) support the development of new Responsible Research and Innovation (RRI) and Open Science (OSc) strategies and guidelines, in the context of safe spaces to involve and engage civil society in the whole science process.

Coordinator

FUNDACION PRIVADA INSTITUTO DE SALUD GLOBAL BARCELONA
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Spain

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EU contribution: EUR 229 048,75

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Permalink: http://cordis.europa.eu/project/rcn/210055_en.html

GCOF

Project ID: 643439
Funded under: H2020-EU.3.1. - SOCIETAL CHALLENGES - Health, demographic change and well-being

A stepping stone approach towards the Genetics Clinic of the Future

From 2015-01-01 **to** 2017-06-30, closed project

Project details

Total cost:	**Topic(s):**
EUR 1 195 106,25	HCO-15-2014 - Mobilisation and mutual learning action plan
EU contribution:	**Call for proposal:**
EUR 1 195 106,25	H2020-HCO-2014 See other projects for this call
Coordinated in:	**Funding scheme:**
Netherlands	CSA - Coordination and support action

Objective

The Genetics Clinic of the Future (GCOF) project aims to ensure that the clinical implementation of genome technologies is relevant and responsive to the needs of all. It offers a stepping stone approach towards the genetics clinic of the future, engaging all stakeholders involved in a process of mutual learning and information exchange.

The GCOF project implements key Science with and for Society issues, ensuring that ethical reflection and stakeholder involvement do not occur in parallel, but are effectively integrated in the core of the project. It establishes a robust communication and implementation strategy that integrates the project's outcomes and recommendations in research and clinical practices and policy processes, outlining opportunities for a more responsive health research and innovation system by:
1. Envisioning the Genetics Clinic of the Future (WP1)
2. Mapping out the concept of data control (WP2)
3. Considering ethical and legal dimensions in the consent framework (WP3)
4. Exploring novel models for use of clinical data in research and vice versa (WP4)
5. Initiating public engagement, mutual learning and dissemination (WP5)
6. Engaging policy makers (WP6)

The consortium brings together 12 key partners from 10 countries across Europe who represent the breadth of stakeholders involved in the genetics clinic of the future: genomics research, clinical genetics, bioinformatics, public health, policy making, patient representation, education, commercial genetics and bioinformatics services, social research, communication, responsible innovation and ethics and law. The GCOF project connects to the major EU-initiatives in the field of personalised health and care. The consortium also represents a variety of organisation types, including research organisations, businesses, policy makers, civil society organisations, education establishments and science & society centres.

Related information

Top Stories	Periodic Reporting for period 1 - GCOF (A stepping stone approach towards the Genetics Clinic of the Future)

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EU contribution: EUR 67 062,5

Last updated on 2017-03-29
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Permalink: http://cordis.europa.eu/project/rcn/194066_en.html

ETHICAL RISK

Project ID: 301816
Funded under: FP7-PEOPLE

An ethical framework for the risk-based regulation of biomedical research

From 2013-09-15 **to** 2015-09-14, closed project

Project details

Total cost:	**Topic(s):**
EUR 209 033,4	FP7-PEOPLE-2011-IEF - Marie-Curie Action: "Intra-European fellowships for career development"
EU contribution:	**Call for proposal:**
EUR 209 033,4	FP7-PEOPLE-2011-IEF See other projects for this call
Coordinated in:	**Funding scheme:**
United Kingdom	MC-IEF - Intra-European Fellowships (IEF)

Objective

Background: Biomedical research has important social and economic value. It helps to promote individual and population health, boosts competitiveness and innovative capacity, and thereby contributes to economic growth. Yet, biomedical research exposes study participants to risks. Research also poses risks to public health when the science is poor. The ethical acceptability of research therefore critically depends on protecting participants' rights and safety, while promoting the scientific and social value of the research. Research regulations are designed to ensure that these requirements are met. -- Patient organizations, investigators, sponsors, and others are increasingly dissatisfied with the existing regulatory framework. Many call for a "risk-based" system of research oversight that matches various safeguards – including independent ethical review and safety monitoring and reporting – to the level of risk posed by the research (e.g., revision of the EU Clinical Trials Directive). However, it remains unclear what such a system should look like.

Objectives: 1) To address the ethical questions raised by risk-based research regulations, including the stratification of research risks and the relation between risk, consent, and the scientific and social value of the research. 2) To develop an ethical framework for risk-based research regulations.

Methods: Interdisciplinary study that combines conceptual and normative analysis, policy analysis, and expert consultation.

Target audience: Policymakers, research regulators, research ethicists, and others interested in the ethics and regulation of risk.

Impact: By calibrating safeguards and protections to the level of risk posed by a study, the envisioned framework will help to promote valuable research consistent with adequate subject protection. This is a prerequisite for responsible progress in health. The project will inform current policy and ethical debates both on a national and international level.

Related information

Result In Brief	An ethical framework for the regulation of biomedical research

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Subjects

Scientific Research

Last updated on 2016-04-01
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Permalink: http://cordis.europa.eu/project/rcn/106420_en.html

CONTRACT

Project ID: 261412
Funded under: FP7-HEALTH

Consent in a Trial and Care environment

From 2010-10-01 **to** 2012-09-30, closed project

Project details

Total cost:	**Topic(s):**
EUR 581 792,4	HEALTH.2010.4.2-6 - Impact of EU legislation on health research. FP7-HEALTH-2010-single-stage
EU contribution:	**Call for proposal:**
EUR 499 235	FP7-HEALTH-2010-single-stage See other projects for this call
Coordinated in:	**Funding scheme:**
Germany	CSA-SA - Support actions

Objective

CONTRACT is about consent. The project focuses on analysing how the legal (and underlying ethical) concepts of informed consent in the European Data Protection Directive and in the Clinical Trials Directive have had and continue to have an impact on the success of translational research. The project predominantly deals with vulnerable patients as their consent is of utmost complexity.
The concept of informed consent in the two mentioned Directives will be analysed from a legal, ethical, IT-related and clinical point of view. The European approach on the matter will be compared with national concepts of informed consent for care purposes in the Member States.
CONTRACT will support the European Commission and other policymakers in achieving a clear Community framework by providing clarity on different concepts of informed consent on European and national level. CONTRACT's approach will be based on facts and figures by delivering an empirical survey about the handling of consent in European and national translational trials. CONTRACT will identify good practices in obtaining and administering informed consent in translational research and will give recommendations on possible harmonization of and common approaches to the legal framework.
CONTRACT has already built a target community for its services, the "partner projects", which will be significantly enlarged after the project's start. CONTRACT will offer a help desk for its target audience on consent issues and will constantly support partner projects and other relevant stakeholders in balancing patient's and research interests by a proper management of consent.
In achieving these objectives the project has put together an internationally recognised interdisciplinary team of individuals and organisations with significant expertise and know-how on all areas of relevance to the project, it has drawn-up a ambitious – yet achievable - workplan, and has made every effort to identify and minimize potential risks.

Related information

Result In Brief	Respecting informed consent, protecting patient rights
Report Summaries	Final Report Summary - CONTRACT (Consent in a trial and care environment)

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Subjects

Life Sciences - Medical biotechnology - Medicine and Health

Last updated on 2017-05-26
Retrieved on 2017-08-07

HLREADGR

Project ID: 518711
Funded under: FP6-MOBILITY

Health Literacy, readability, and informed consent in Greece & Europe

From 2006-09-01 **to** 2008-08-31

Project details

Total cost:	**Topic(s):**
Not available	MOBILITY-4.1 - Marie Curie European Reintegration Grants (ERG)
EU contribution:	**Call for proposal:**
EUR 80 000	FP6-2004-MOBILITY-12 See other projects for this call
Coordinated in:	**Funding scheme:**
Greece	IRG - Marie Curie actions-International re-integration grants

Objective

The importance of health literacy has been established in medical literature in relation to health behaviour motivation and health outcomes, but little is known about health literacy in Europe including Greece. People with low health literacy are likelier t o report poor health, likelier to not fully understand their health problems and treatment, and are at higher risk for hospitalisation. Little has been done in Europe regarding the importance of readability and health literacy for improving patient outcome s and the relation of the former to informed consent and other medical documents. Most readability formulas have been created and tested in the English language and health literacy research has mainly been done in the U.S.

The project will begin by "mapping " identified European researchers working and conducting research in the above areas, including health literacy and informed consent, as this process allows for shared ideas and knowledge. This project will focus on exploring current readability formulas f or the English language as applied in the Greek language, including developing and pilot testing a new readability formula for the Greek language. This new formula will be applied to different patient educational and research tools with a special focus on informed consent forms. Two consent forms from public or private medical centre studies will be identified and their consent forms will be evaluated using our new readability formula. Patients' understanding of the studies' components will be examined and the extent to which a signed informed consent reflects reality. Additional forms for potential evaluation include disease management information sheets and brochures.

The project's overall goal is to develop and integrate methods for the "informed patient," thus, improving the communication among health care providers, health educators, and patients, which may lead to better health care quality and improved patient outcomes.

Related information

Report Summaries	Final Activity Report Summary - HLREADGR (Health literacy, readability, and informed consent in Greece & Europe)

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Last updated on 2009-09-29
Retrieved on 2017-08-07

Permalink: http://cordis.europa.eu/project/rcn/81093_en.html

ED-REG-HAR

Project ID: 509551
Funded under: FP6-MOBILITY

Ethical diversity and regulatory harmonisation: an empirical exploration of research ethics committees following the directive on good clinical practice

From 2004-10-01 **to** 2007-09-30

Project details

Total cost:	**Topic(s):**
Not available	MOBILITY-3.1 - Marie Curie Excellence Grants (EXT)
EU contribution:	**Call for proposal:**
EUR 1 076 871	FP6-2002-MOBILITY-8 See other projects for this call
Coordinated in:	**Funding scheme:**
United Kingdom	EXT - Marie Curie actions-Grants for Excellent Teams

Objective

The aims of this project are: to explore the way in which Independent Ethics Committees (IECs) assess clinical trials protocols for ethical suitability; to assess which variations are necessarily a consequence of local cultural differences, and which are not; to highlight the way in which European pharmaceutical harmonisation can incorporate ethical diversity and develop best practice for IECs.

As a result of the Directive on Good Clinical Practice (GCP), since the 1st of May 2003 Independent Ethics Committees have had a statutory role under European Legislation in the ethical assessment of clinical drugs-trials. This is part of a general move towards the harmonisation of pharmaceutical regulations, both worldwide and within Europe (e.g. the setting up of the EMEA).

But there is a largely unexplored tension between this drive towards harmonisation, now seen in ethical review, and the important role cultural and ethical diversity plays within Europe. For example, even within a single member state (the UK), there has bee n considerable tension between the requirement that clinical trials be assessed by ethics committees and the range and diversity of opinion such committees have, even regarding the same clinical trial.

This problem will be magnified at the European level. This project will use qualitative methods to compare the decision-making processes of ethics committees in four different countries (UK, Sweden, Portugal and Hungary). The team will recruit a researcher from each of these countries, showing a high degree of mobility.

In its analysis the team will use dimensions of comparison such as: differing interpretations of what is meant by informed consent; the relationship between need for technical ability to understand material and the democratic principle of lay members; and the influence of different cultural/social factors (e.g. religious traditions;

Related information

Report Summaries	Final Activity Report Summary - ED-REG-HAR (Ethical diversity and regulatory harmonisation: an empirical exploration of research ethics committees following the Directive on Good Clinical Practice)

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Retrieved on 2017-08-07

Permalink: http://cordis.europa.eu/project/rcn/80764_en.html

EURICON

Project ID: BMH4950169
Funded under: FP4-BIOMED 2

Is obtaining informed consent for neonatal research an 'elaborate ritual'? A european study

From 1995-12-01 **to** 1998-11-30

Project details

Total cost:	**Topic(s):**
Not available	8.1 - Ethical, legal and social aspects
EU contribution:	**Funding scheme:**
Not available	CON - Coordination of research actions
Coordinated in:	
United Kingdom	

Objective

This proposal sets out to do this and in summary aims:
to investigate the extent to which European countries differ in the legal and ethical guidelines they impose regarding the obtaining of informed consent for research on neonatal units; to analyse the possibility of harmonization; to seek to develop proposals to that effect;
to determine the validity of the consent process from the view point of clinicians and also parents of babies who were previously on a neonatal unit;
to examine the European legal and ethical guidelines in the light of any practical difficulties in applying these guidelines as assessed above.

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Subjects

Legislation and Regulations - Life Sciences - Medicine and Health - Social sciences and humanities

Last updated on 1998-10-05

Basic ethical pinciples in bioethics and biolaw

Project ID: BMH4950207
Funded under: FP4-BIOMED 2

Basic ethical pinciples in bioethics and biolaw

From 1995-12-01 **to** 1998-11-30

Project details

Total cost:	**Topic(s):**
Not available	8.1 - Ethical, legal and social aspects
EU contribution:	**Funding scheme:**
Not available	CON - Coordination of research actions
Coordinated in:	
Denmark	

Objective

Basic Ethical Principles in Bioethics and Biolaw is orientated towards clarifying the conceptual basis for the ethical and legal measures which direct the development and use of biotechnologies in medicine and health research. It examines the extent to which different basic ethical principles are linked to particular cultural traditions and to particular social groups; the extent to which they can be used to mediate ideas of universal value in pluralistic societies characterised by a diversity of norms, and as moral prescriptions directed towards a certain harmonisation, respecting historical and cultural differences of bioethical and biolegal policies in Europe. The investigation relies on the concerted actions of experienced researchers, sociologists and ethical theorists in different countries and local cultures in Europe.

To provide early warnings of new bioethical issues in society, and especially of popular resistance against biotechnologies, it is necessary to reflect on the principles which signify that one should respect and protect individuals in the areas of medical and biological research, health and health care. Reference is often made to the autonomy of the patient and of the subject of medical experiments in order to prevent violations of persons. It has been claimed that their 'informed' or 'presumed' consent must be assured. But, more and more, especially amongst physicians and ethicists, there is an awareness of the limitations on the principle of autonomy as such. Some individuals, including children and people with a mental handicap, are not able to protect themselves.

This does not mean that the principle of autonomy should be left aside, but it necessitates both concrete and theoretical examination of classical or more recent principles, which have validity as complementary and even, in certain cases, as alternatives to the principle of autonomy to express the foundation or the rationality of respect and responsibility towards human beings. Three principles must certainly be subject to careful scrutiny: the principles of dignity, integrity and vulnerability.

The project will involve a series of theoretical tasks, examining these issues of principle as well as certain legal frameworks; a series of concrete tasks examining the application of various ethical principles in certain bioethical fields; the establishment of a Documentation Centre for European Bioethics and Biolaw; and the publication of a newsletter which it is intended should be developed into a Journal of Bioethics and Biolaw in Europe.

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Subjects

Legislation and Regulations - Life Sciences - Medicine and Health - Social sciences and humanities

Last updated on 1998-03-25
Retrieved on 2017-08-07

Permalink: http://cordis.europa.eu/project/rcn/38447_en.html