

# Informed Consent in Clinical Studies

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## Abstract

Informed and voluntary consent are important aspects that should be considered when conducting human research. The importance of this has come to the forefront particularly since the atrocities of World War II. Since, there have been numerous legal additions to safeguard research volunteers and ethical approval applications also incorporate this process. Consent is therefore one of the nuts and bolts of research methodology.

This article looks at the informed consent process and at how this is obtained. It discusses how research informed consent varies from consent for a clinical procedure and looks at occasions when this important aspect can be waived.

## Main Text

Informed and voluntary consent are important aspects to consider when conducting human research. The Nuremberg Code<sup>1</sup>, The Declaration of Helsinki<sup>16</sup> and The Belmont Report<sup>17</sup> all support this key aspect.

The Nuremberg Code<sup>1</sup> a set of 10 ethical principles, is laid out following the atrocities of World War II to protect fellow humans who take part in medical experimentation. The first principle of this code is about 'voluntary consent'. The Nuremberg Code<sup>1</sup> highlights that a person must have 'legal capacity to give consent'. This not only spells out that an assessment of capacity is necessary but also has implications in studies involving children, adolescents and vulnerable adults. Capacity is a time and decision specific assessment of the person's understanding, ability to retain, weigh and communicate the information and their decision. A capacity assessment is more complex in children as one must consider their level of psychological development, their understanding of the decision as well as the views of the parents.<sup>2</sup> Following the Gillick ruling, it must be noted that children, even under the age of 16, have the capacity to consent to treatment, even if their parents do not consent.<sup>3</sup> Whilst this is used in medical care, in most circumstances Gillick competency is not extrapolated to medical research.<sup>4</sup>

Another important aspect of The Nuremberg Code (1947)<sup>1</sup> is that a person must have the 'free power of choice'. This means that they are not to be constrained or coerced in any way to join the study. It expands on the meaning of obtaining informed consent - that is that a person must be given enough information to ensure that they can take 'an understanding and enlightened decision'.<sup>1</sup> This means that a person must know the nature of the clinical trial, expected length of time during which the research will be undertaken, the aims and objectives, the way in which the trial will be conducted, any adverse effects or risks as well as potential benefits and alternative therapies/treatment options to the one under investigation. All these aspects, form the basis of the Integrated Research Application System (IRAS) form. This is the form through which ethical approval is requested - and this must be obtained prior to the commencement of a clinical trial. Finally, The Nuremberg Code (1947)<sup>1</sup> also

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stipulates that the process of ascertaining informed consent is the role of the chief investigator and emphasises that this role cannot be delegated.

The Declaration of Helsinki,<sup>16</sup> underwritten by the World Medical Association, further expands on The Nuremberg Code. It explains why human research is needed but emphasises that despite this, the person's health must remain the priority.<sup>5</sup> It acknowledges the patient's right to withdraw from a study and this may occur at any stage of the clinical trial. The Declaration of Helsinki also mentions the concept of assent, whereby participants who are not able to give informed consent (and therefore need a third party to do so on their behalf - this may include children and people with learning disability, amongst others) should still agree to participate in the clinical trial/research.<sup>5</sup>

The Belmont Report<sup>17</sup> emphasises the principles of beneficence, justice and respect.<sup>6</sup> Within this, it describes the participant as 'autonomous', meaning that they can choose whether they would like to be part of a trial or otherwise. This forms the crux of informed consent. Furthermore, it stipulates that people with diminished capacity should be given additional safeguards.

Informed consent should include information on premature termination of a clinical trial and this should only occur for efficacy, safety or feasibility reasons.<sup>22</sup> The informed consent process is usually evidenced with signed consent documentation. However, there are occasions when this may not be possible. This does not preclude that the person does not receive the necessary information to make the decision is given, but waives the need for signed documentation. This may be necessary to safeguard the person if the research is about sensitive topics (such as domestic violence research) or in research whereby there is "no more than minimal risk of harm to subjects"<sup>7</sup> or when written consent is not usually required for such procedure. This usually encompasses telephone and web-based surveys.<sup>7</sup>

This begs the question - can informed consent be waived? There are some instances where some or all aspects of informed consent can be waived.<sup>8</sup> The Common Rule in the United States<sup>9</sup> identifies 4 main occasions where this can be waived, that is:

1. There is minimal risk;
2. The resulting waiver does not affect the rights or well-being of the people involved in the

research;

3. The waiver is needed for the practicality of the research methodology;
4. Additional information is provided to the people involved in the research after this is carried out (where practical).

Minimal risk is basically day-to-day risk, that we all could face as we go about our daily living. These risks are so commonplace, that we don't usually think about these.<sup>10</sup> In research terms, educational/public health or routine care aspects are examples that would be included under this umbrella.<sup>8</sup> When thinking about methodology, certain modalities of data collection, such as surveys or reviewing medical notes, can also be regarded as minimal risk.<sup>11</sup>

On an aside, both healthy volunteers and patients may receive payments, incentives or expenses payments for their participation in the clinical trial. This should not be related to risk. All payment information should be given to the participants and included in the patient participation leaflet.<sup>23</sup> The Health Research Authority (UK) has issued specific guidance around payment and incentives in relation to research.<sup>23</sup>

The second aspect of when informed consent can be waived goes hand in hand with minimal risk. It relates to ensuring that the resultant waiver does not go against the laws of the state or affect the person's health, finance or legal aspects.<sup>8</sup>

Some research methodologies make obtaining informed consent difficult - such as studies involving cluster level interventions or with large cluster sizes.<sup>8</sup> Another possibility whereby gaining informed consent may be tricky is if the information disclosed during this process were to cause a bias either to the outcomes of the research or cause selection bias.

It is very important to treat the 'research subjects' as individuals and in a humane way. This therefore implies that even if approval is granted on the basis that informed consent is not possible, it is still important to make the information on the study available (e.g. through leaflets, website links) to the potential subjects.<sup>8</sup> Consideration should be made to ensure that this information is explained in a way that the persons involved in the study understand.

One of the functions of informed consent is to allow the people involved in the study (and those treated at a later stage - i.e. after the publication of

that study), to benefit from the study outcomes. This justifies their risk exposure for the benefit of the general population.<sup>8</sup>

So far we have talked about informed consent as a whole, but we must also consider the timeliness of that consent, that is, whether this should be done before or after the randomisation process. Good practice is for informed consent to be sought early on in the study.<sup>8</sup> During randomised control trials (RCTs) the earliest opportunity is before the randomisation process whereby information will be provided about the different arms of the study. Moreover information about the study and expected outcomes as a whole should also be given. It is of paramount importance that comprehensive, honest and accurate information is given.

However, if randomisation has taken place prior to consent being sought, as can be the case in cluster randomised controlled studies (C-RCTs), then the information given can be tailored to the relevant arm that the person has been allocated to.<sup>8</sup> In this case, it is thought justifiable to mention the generic study interventions and aims but not to give specific details about the study and the other arms as this lessens the likelihood of bias.<sup>8</sup>

In some C-RCTs obtaining informed consent prior to randomisation may be difficult<sup>12</sup> and this can raise ethical controversies.<sup>13</sup> Some researchers insist that if the C-RCTs are assessing routine care and are associated with minimal risk this may preclude the need for informed consent,<sup>14</sup> and others state that not obtaining consent prior to randomisation is ethical so long as this is obtained prior to the start of the study and the data collection.<sup>8</sup> The counter-argument to this is an ethical one, with some researchers insisting that the difficulty of obtaining informed consent in C-RCTs should be managed by improving the structure around obtaining informed consent.<sup>12</sup> The 1991 International Guidelines for Ethical Review of Epidemiological Studies state:

*“When it is not possible to request informed consent from every individual to be studied, the agreement of a representative of a community or group may be sought... Approval given by a community representative should be consistent with general ethical principles... A leader may express agreement on behalf of a community, but*

*an individual’s refusal of personal participation is binding” (15: p. 225-226).*

In essence it is clear that the informed consent process is important. It ensures that participants have enough information and understanding to make a decision as to whether they want to enter a clinical study that is in line with their beliefs, values and culture. However as there are some exceptions when this can be waived, informed consent is not an absolute criterion. It remains however, a critical aspect that must be considered when conducting clinical studies.

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