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<https://orcid.org/0000-0003-4455-1704>**MacCAT-CR: a way to legitimate the informed consent process in clinical research***MacCAT-CR: uma forma de legitimar o processo de consentimento informado na pesquisa clínica*

**Abstract:** Informed consent is an essential ethical component of clinical trials, however, there are still many doubts about its proper realization nowadays. Consent is usually obtained formally, but there are doubts about the competence of participants in a clinical trial to decide whether to participate. From there, a concern arises with the use of instruments capable of assessing the participants' competence to express a decision. The MacArthur Competence Assessment Tool (MacCAT-CR) can be considered as an appropriate tool for assessing the informed consent process, as it can evaluate participants' ability to express a decision about their participation in each clinical trial. We review the application of MacCAT-CR in studies involving participants without cognitive impairment, representative of most individuals who generally participate in clinical trials. Our results demonstrate that few studies are evaluating the use of this tool to assess the competence of reasonable participants since most studies are focused on evaluating the consent process in individuals with limited autonomy. Here we discuss the ethical relevance of ensuring that the autonomy of research participants is manifested by assessing the effectiveness of the consent process, especially in developing countries.

**Keywords:** Informed Consent. Clinical Trials. Research Ethics. Autonomy.

**Resumo:** O consentimento informado é um componente ético essencial dos ensaios clínicos, entretanto, existem muitas dúvidas sobre sua realização adequada nos dias atuais. O consentimento geralmente é obtido formalmente, mas há dúvidas sobre a competência dos participantes de um ensaio clínico em decidir sobre a sua participação. A partir daí, surge a preocupação com a utilização de instrumentos capazes de avaliar a competência dos participantes para expressar uma decisão. O *MacArthur Competence Assessment Tool* (MacCAT-CR) pode ser considerado uma ferramenta apropriada para avaliar o processo de consentimento informado, pois pode avaliar a capacidade dos participantes de expressar uma decisão sobre sua participação em cada ensaio clínico. Revisamos a aplicação do MacCAT-CR em estudos envolvendo participantes sem comprometimento cognitivo, representativos da maioria dos indivíduos que geralmente participam de estudos clínicos em países em desenvolvimento. Nossos resultados demonstram que poucos estudos avaliaram o uso dessa ferramenta aplicada a indivíduos representativos dos participantes dos estudos clínicos, uma vez que a maioria das publicações estão voltadas para a avaliação do processo de consentimento em indivíduos com autonomia limitada. Discute-se a importância ética em garantir que a autonomia dos participantes da pesquisa se manifeste por meio da avaliação da eficácia do processo de consentimento, especialmente em países em desenvolvimento.

**Palavras-chave:** Consentimento Informado. Testes Clínicos. Ética em Pesquisa. Autonomia

## Backgrounds

### Informed Consent

Informed consent is one of the most important ways to respect the bioethical principle of autonomy in clinical research. Informed consent is a process whereby participants are informed about the research objectives, procedures, risks and benefits, and are invited to make an informed and voluntary decision about their participation (Paris et al, 2010; Desch et al, 2011).

By providing detailed information about the research and allowing participants to make informed, voluntary decisions about their participation, informed consent helps to respect the bioethical principle of autonomy. It recognizes the right of participants to make informed and voluntary decisions about their participation and ensures that their decision is respected by researchers and other professionals involved in the study (Spatz, Krumholz, Moulton, 2016; Hochhauser, 1999, Rodrigues Filho, Prado, Prudente, 2010).

In addition, informed consent helps ensure the validity of research results, as participants will be more motivated and engaged in following research procedures and providing accurate and reliable information. This helps ensure the integrity of the survey and increases the reliability of the results obtained (Jeste et al, 2007).

Informed consent is an essential way of respecting the bioethical principle of autonomy in clinical research. It helps ensure that participants make informed, voluntary decisions about their participation, respecting their rights and interests, and contributes to the validity and integrity of research (Supady et al, 2011).

International guidelines require that the informed consent of all enrolled participants is obtained. So far, a document must be written (Informed Consent Form) describing all information needed, but some studies show that this document has grown too hard, in linguistic and technical language, focusing on judicial protection to the researchers, institutions, and sponsors. Also, readability tests, such as Flesch–Kincaid Grade Level, have shown that these documents are often not accessible to the understanding of many typical participants of clinical trials, mainly in developing countries where the clinical trials typical participants have low educational grade levels (Rodrigues Filho, Prado, Prudente, 2014; Paris et al, 2010).

Many strategies are being proposed to mitigate this problem, such as the use of multimedia and flyers, to give participants necessary information about the research procedures and the conditions of their participation in the trial. This situation is not limited to a single country or region, since the USA, South America, Europe, and Asia have reported the same issues (7–13). Furthermore, the objective of the Informed Consent Form is to formalize the process of informed consent and make available to the participant all relevant information about the benefits, risks, study procedures and other relevant information about their participation in a trial (Rodrigues Filho, Prado, Prudente, 2014; Paris et al, 2010; Murray, 2012).

Some researchers argue that it is unviable to perform research without the application of this document to formalize the consent of participants, on the other hand, some try to find alternatives to improve the informed consent process, and others propose the simple removal of this document from the process (Spatz, Krumholz, Moulton, 2016; Jeste et al, 2007; Henry et al, 2009; Fanaroff et al, 2018).

Regardless of the context in which the informed consent process is applied, it is important to consider tools that can ensure that the participant can consent to their participation in a study (Spatz, Krumholz, Moulton, 2016; Fanaroff et al, 2018).

Taking into account the Kantian ethics, without a clear understanding of the information provided, even considering individuals with full cognitive ability, it is not possible to say that their decision will be autonomous, because there was no proper clarification. Some studies have shown that the ability to understand a given scenario greatly affects various individual skills, including decision-making. In the specific case of the decision to take part in a clinical trial, it seems that sometimes even without understanding the conditions of their participation, most of the participants agree to participate. This can be caused, among other things, by fear of undermining the relationship between health professionals and a trial participant's (Paris et al, 2010, Rodrigues Filho, Prado, Prudente, 2014; Miranda et al, 1992). So, it seems clear that even when the current legal and ethical frameworks are applied, it is not possible to assure that the formalized consent corresponds to a decision that has taken into account the autonomy of the individual and thus proposes the use of instruments that can assess the competence to exercise such autonomy is very important.

## Autonomy

The principle of autonomy is a foundational ethical concept in clinical research that acknowledges participants' right to make informed and voluntary decisions about their participation, which must be respected by the researchers and other professionals involved in the study (Rodrigues Filho, Prado, Prudente, 2014; Appelbaum, Griso, 2001). The significance of this principle can be observed in multiple aspects:

**Protection of Participants' Rights:** The principle of autonomy safeguards participants' rights and interests by ensuring that they are not coerced or pressured to participate in research and are able to make informed and voluntary decisions (Ossemane et al, 2018).

**Promoting Public Trust in Research:** When researchers uphold the autonomy of participants, it fosters public trust in clinical research, increasing individuals' willingness to participate in studies and advancing scientific and medical knowledge (Hochhauser, 1999; Cohn et al, 2011).

**Assurance of Validity of Research Results:** When participants are empowered to make informed and voluntary decisions about their participation, it enhances the validity of research results. Participants who are well-informed and voluntarily engaged in the research are more likely to follow research protocols and provide reliable and accurate data, contributing to the integrity of the research (Paris et al, 2010; Anandaiah, Rock, 2019).

**Harm Prevention:** The principle of autonomy assists in preventing unnecessary harm by allowing participants to make informed and voluntary decisions about their participation. By having access to comprehensive information, participants can make decisions that align with their needs and preferences, reducing the likelihood of harm (Paris et al, 2010; Murray, 2012; Spatz Krumholz, Moulton, 2016; Hochhauser, 1999).

The principle of autonomy is essential to ensure that participants in clinical trials are treated with respect and dignity, and that their participation is voluntary and informed. It helps protect your rights and interests, promotes public confidence in research, ensures the validity of results, and helps prevent unnecessary harm.

## MacCAT-CR

The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) is a structured interview that allows the researcher to access and evaluate the decision-making capability of a participant to consent to their participation in a trial, taking into account four aspects: “Understanding” if the information has been transmitted; “Appreciation” if the participant can think about the effects of the research purpose; “Reasoning”, that evaluates the participant ability to compare alternatives with their consequences and finally “Expressing a decision” about his participation on a trial (Appelbaum, Griso, 2001). This instrument, developed in English, is already translated and adapted to Spanish and Chinese, but not in other languages or cultural contexts (Appelbaum, Griso, 2001; Lan et al, 2013, Baón-Pérez et al, 2013).

MacCAT-CR authors also emphasize that their instrument has been developed as a tool to enhance the protection of research participants, promoting the legitimization of the informed consent process (Appelbaum, Griso, 2001).

The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) is a reliable and standardized instrument designed to evaluate a participant's capacity to comprehend the research's nature, potential benefits and risks of participation, available alternatives, and ramifications of non-participation (Appelbaum, Griso, 2001). This assessment tool enables researchers to identify individuals who may encounter challenges in making informed decisions and require additional assistance in comprehending the provided information and deciding whether to participate in the study.

Here, we reviewed studies that assessed the application of the MacCAT-CR to assess the competence of typical participants to consent to their participation in clinical studies and discussed the importance of using instruments to ensure the exercise of autonomy by participants in clinical studies.

## Methods

This systematic review is consistent with existing reporting guidelines - the PRISMA statement (Moher, Liberati, Tetzlaff, Altman, 2009).

### Eligibility criteria

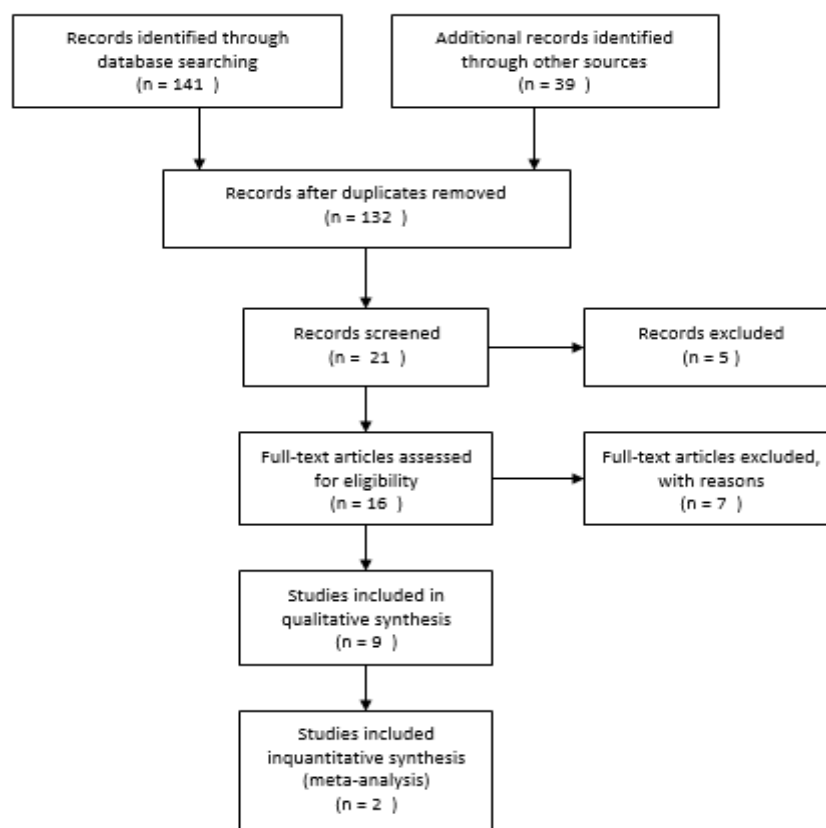
We included articles that used MacCAT-CR to evaluate the informed consent process with reasonable participants in real and fictional clinical trials. We excluded

case reports, single cohort studies, non-randomized trials, and systematic reviews that enroll participants with Alzheimer's Disease, Parkinson's Disease, chemical dependence, and other pathological conditions that could lead to impairment of autonomy. Articles that enroll children, adolescents, adults, and elderly individuals, were included (Figure 1).

### Search strategy

The research was conducted in databases through the last 10 years in the "Periodicos Capes" database (Brazil) and PubMed Database, using the keyword "MacCAT-CR".

**Figure 1:** Flow-diagram of the systematic review.



**Source:** survey data.

## Results

The selection process is described in Table 1. In sum, twenty-one primary articles were reviewed. As some of these articles tested just cited MacCAT-CR or another modality of MacCAT, we ultimately tracked nine articles that could be included, since they are compatible with our main eligibility criteria.

**Table 1:** Characteristics of studies included.

Author	Trial/Review	Population
Baón-Pérez, et al	Trial	Adults
Gillies, et al	Review and meta-analysis	Adults
Hein, et al	Review	Children
Hein, et al	Trial	Children
MacGregor, et al	Trial	Adolescents
Nelson, et al	Trial	Adolescents
Nishimura, et al	Review and meta-analysis	Adults
Michaud, et al	Review	Adolescents
Suhonen, et al	Review	Older People

**Source:** survey data.

Five studies used MacCAT-CR to evaluate the capability of the participants expressing decisions after the process of informed consent. Four of them were real (not fictional) clinical trial studies. One was a study that evaluated the MacCAT as a tool to assess whether participants were able to express a decision about donating blood samples.

Four studies were reviews, two of them were a meta-analysis that compares the feasibility of MacCAT-CR, with other validated instruments to evaluate the informed consent process.

### **Clinical trials**

Four clinical trials used an adaptation of MacCAT-CR to access a regular informed consent process in adolescents and children, as this instrument was not developed for this population. They found that adolescents in grades 8 to 9 (US system) were able to express a decision. In these studies, it was demonstrated that the family environment, in addition to the level of education in general, can give these adolescents a decision-making competence like that of adults. In addition, children with 11 years old and older were also able to understand and express consent, while children under 9 were unable to. These studies tend to point out that age seems to be a determining factor in promoting decision-making competence and emphasizes the importance and relevance



of MacCAT-CR for use in similar situations. One study aimed to validate the tool for Spanish and discussed the importance of a tool to improve the ethically appropriate conduct of the informed consent process (Baón-Pérez et al, 2017; McGregor, Ott, 2019; Hein et al, 2015; Hein et al, 2012; Nelson, Stupianski, Ott, 2016).

## Reviews

One review stated the key factors to reach the consent of a child to clinical research. There are factors that have influenced this competence: age, development stage, the influence of parents and relatives, and life experience. They found that the level of education of the parents influenced children's understanding (Suhonen, Stolt, Launis, Leino-Kilpi, 2010; Hein et al, 2015).

In this review, considering studies that enroll children and establish age limits as criteria became a huge challenge because they found a significant difference regarding the factors that influence the children's competence to express a decision. They also attempted to obtain an informed consent standard based on the age of the individuals but concluded that further studies are needed (Hein et al, 2015).

Other reviews assessing adolescents' consent, pointed out additional aspects to be considerate. Legally their rights are the same as children's rights, so the researchers who conduct the informed consent process tend to treat adolescents as children. For this reason, adolescents may refuse to participate in a trial due to the feeling that the decision was made by someone else, such as relatives, compromising their autonomy to make their own decision (Michaud et al, 2018).

Therefore, an assessment of an adolescent's decision-making process may be essential. In this article the ethical challenges of research that enrolls adolescents were discussed, emphasizing that a different approach could bring benefits to facilitate the decision of these individuals (Michaud et al, 2018).

## Meta-Analysis

Both meta-analyzes consider the evaluation of informed consent to be a subjective process, recognizing this factor as being associated with possible difficulties. Each informed consent process is generally specific to a specific population or clinical condition of the participants and is also conditioned by the objectives of the researchers. They argue that there are five main domains in obtaining consent: the autonomy of the participant: evaluation of the consequences, expectations of the participant, objective



of the researcher, and individualized approach. These factors must be considered in the informed consent process, as well as in the corresponding informed consent form. These articles emphasize that running an informed consent process based on concepts and conceptualized on these five main factors can improve the entire process. MacCAT-CR appears to be the only tool that includes all five domains and covers any cognitive aspect to achieve understanding, appreciation, reasoning and decision making (Gillies, Duthie, Cotton, Campbell, 2018; Nishimura et al, 2013).

The authors stated that the informed consent process is the cornerstone of clinical research. They studied interventions to improve the informed consent process to make the process more ethically appropriate and found that MacCAT-CR was the most complete, viable, and reliable tool for evaluating the process.

Several elements were recognized as essential for carrying out an appropriate informed consent process: controlling the process (taking into account the environment, helping the participant and giving the participant the feeling that the researcher is accessible); adjust the readability of the consent form to the capacity of the population participating in a trial and, as mentioned above, the difficulty of standardizing informed consent (Gillies, Duthie, Cotton, Campbell, 2018; Nishimura et al, 2013).

## Discussion

Informing a participant faithfully is essential to conduct ethical research. It is unthinkable that consent could be given by anyone unaware of the conditions of their participation in each research. The fundamental purpose of the informed consent process is to provide the participants with the necessary and relevant information; however, as it is often conducted in different ways, sometimes inappropriately, it is required to use instruments that can assess whether the participant acquired the competence to decide. Participants generally tend to agree to participate in a trial, even if they are unsure of the actual conditions of their participation, including potential risks and benefits. It is a fact that a clinical trial, for example, involving testing of new drugs or medical procedures, can have unpredictable consequences, which makes it difficult for the participant to decide, even when they are submitted to an appropriate consent process (Supady et al, 2011).

Researchers cannot expect participants to fully exercise their autonomy without

understanding all the information needed to express a decision, and this is a matter of concern. There are several regulatory frameworks, laws, and guidelines related to respect for research participant autonomy. It must be considered that all studies have their singularities, which bring barriers to finding a general model for the application of the informed consent process, that can contemplate the participants' individualities.

It should be emphasized that autonomy depends on clarifying, which can be defined here as not only providing the information but properly understanding that information. It is worth recalling Kant's contribution to the understanding of autonomy, who in his *Grounding of the Metaphysics of Morals* proclaims that a morally evaluable action "depends on wanting - according to which action, abstracting from all objects of the aptitude of desire - was practiced" (Kant, Ellington, Kant, 1993). Without clarification, there would be no autonomy, because its basic principle is lacking, and so individuals cannot make a free decision because they are subject to heteronomy (others must think for the individual or have the knowledge that they do not have, but that is necessary for the decision to be free). In this sense, not only individuals with cognitive disabilities but also reasonable participants of a clinical trial must undergo an assessment of their decision-making ability, ensuring that their autonomy has been exercised.

Some studies propose alternative ways, such as videos and supplemental materials to inform participants of given research, but again, no effort is made to evaluate whether these mechanisms are effective. Often, the amount of people who agree or not to participate in a trial is the only parameter considered to measure the effectiveness of the informed consent process. In these cases, the agreement of the participants is considered an indicator of their ability to understand their participation conditions.

It should be clarified that the potential for understanding does not imply actual understanding. The principle of Kantian enlightenment is not just potential, but knowledge about what is being decided autonomously (in the opposite meaning of heteronomy).

There are several tools to evaluate the ability of the participants to express a decision about their participation in given research, among them the MacCAT-CR, which was developed by Appelbaum and Griso in 2001 (Appelbaum, Griso, 2001). The results of this review permit us to conclude that this instrument may be adequate to carry out such evaluation.

Not many studies report the use of MacCAT-CR to evaluate the decision-making competence in reasonable participants; however, many studies are reporting its use in individuals with cognitive impairment and vulnerability conditions.

MacCAT-CR is also considered useful for its versatility, feasibility, and accuracy, as its results are expressed in numerical scores. Studies have shown that MacCAT-CR is a complete tool for evaluating the informed consent process. This instrument can adapt to different situations and different groups of individuals. The MacCAT-CR correlates with other tools that assess the informed consent process by evaluating participants' specific skills such as health literacy - REALM (Baker, 2006) and family economic status - FAS (Hobza, Hamrik, Bucksch, de Clercq, 2017).

In emerging countries, typical participants in clinical trials are mostly users of public health systems with socio-demographic characteristics that show low educational levels and social vulnerability. When these factors are considered, it is possible to speculate that these individuals do not fully understand the nature of their participation in the research, mostly when the informed consent process is restricted to reading and signing an extensive document full of technical terms. Moreover, we can speculate that the informed consent process in emerging countries could become such a mere formality.

But that is not all. In these countries, the phenomenon of heteronomy can be hidden in many ways. If researchers lack the virtues necessary to apply the informed consent process, they may induce the participant to agree to take part in the research. In this case, we can say that the decision was not autonomous, because in influencing the decision, the researcher ended up deciding by the participant, since it created a situation, perhaps false, but unequivocally biased, which led to the expression of a non-autonomous decision. Other times the agreement to participate in the research is motivated by the need to obtain a given health treatment that in these countries would not be possible without taking part in a clinical trial. Also, the fear of compromising the professional-patient relationship may be an inductive element for the research participant's decision. As can be seen, heteronomy is not always clearly manifest and can be camouflaged in each situation, which can either be created on purpose or can result from local and specific scenarios.

## Final considerations

Although the studies employed in this research do not explicitly address autonomy, it is evident that the researchers are mindful of this ethical principle as they have chosen to use the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), which is grounded on ethical principles. This tool aims to ensure the preservation of participants' rights, and its usage reinforces the commitment of the study to this fundamental ethical principle. The utilization of appropriate tools humanizes and creates a welcoming environment for the entire informed consent process.

While it may be overly ambitious to assert that the MacCAT-CR instrument can guarantee the autonomy of participants' decision-making in clinical studies, its effectiveness is evidenced in numerous studies. Although the path to legitimizing this process may be challenging and extensive, there is no doubt that it is time to commence this journey.

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