Children's competence to consent to medical treatment or research

Hein, I.M.

Publication date
2015
Document Version
Final published version

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Irma Hein

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The studies described in this thesis were performed at the Department of Child and Adolescent Psychiatry of the Academic Medical Center, University of Amsterdam, the Netherlands. The research project was financially supported by the Netherlands Organization for Health Research and Development.

Lay-out: Crius Group, Hulshout

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het College voor Promoties ingestelde
commissie, in het openbaar te verdedigen in de Aula der Universiteit
op vrijdag 17 april 2015, te 13.00 uur

door Irma Marijke Hein
geboren te Vries

Amsterdam University Press

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Contents

1 Introduction

In the past, children were often excluded from participating in trials out of protection for their well-being, in light of their vulnerability and assumed incompetence. In addition, pharma industry did not want to invest in studies in infants and children as the profits were deemed to be small or even non-existing. This led to a lack of significant research data on the effects of drugs in children, which, inadvertently, places sick children in jeopardy. In daily pediatric practice, patients' competence to consent is usually assessed implicitly because of the assumption that children's ability to understand medical issues is limited.

Strictly speaking, competence to consent denotes a legal status, representing an informed, free, self-determined choice based on understanding and rational reasons.(1) Competence is task and context specific.(1) Incompetence should, in principle, be determined by a court; however, good pragmatic reasons exist to continue the traditional practice of having clinicians determine patients' competence.(2) From a clinical perspective, competence is generally addressed as decision-making capacity,(3) involving factors as developmental stage of children, influence of parents and peers, quality of information provision, life experience, and the type of medical decision to be made. However, law is established on a strong presumption that persons older than a certain age are competent, whereas younger persons are not.

Until recently, there was no empirical evidence on children's competence to consent to treatment or clinical research. The reliability of unstructured competence assessments up to now has been inconsistent, because clinicians possibly did not know which standard to apply,(2) rendering age standards prescribed by law as the guiding principle in their assessments. To complicate matters further, the age limits of these standards for deeming a child competent to consent vary widely between countries.(4) Also, absent a standard, clinicians tended to judge a child competent if the child's decision conformed to their own ideas of what was in the child's best interest.(5)

Therefore, more understanding of the issues involved in children's competence to consent in medical decision-making is needed. The aim of this research is to make recommendations for optimizing policies, in order to do justice to the capacities and challenges children face when deciding about medical treatment and clinical research options. If a fixed age-limit for alleged competence is used, it must be generally in accordance with children's developmental stages. In an ideal situation, statutory

age-limits must accomplish the goal of striking a proper balance in order to both protect children's interests when they are not fully able to do so themselves and to respect their autonomy when they are able to exercise it. Furthermore, for health care professionals as well as pediatric patients and parents, availability of a reliable standard for assessing competence is important.

We attempt to find answers to key questions. What are currently the most efficient practices for assessing children's competence to consent in pediatric practice? Are there any adequate test instruments available, and, if not, could we try to fill this gap? Having an assessment tool at our disposal, which age limits for competence to consent in children can be gathered? And which factors exactly affect children's competence to consent in medical decision-making? Taking into account that recruitment of children for clinical research remains one of the main difficulties, what strategies could optimize research participation of children? Furthermore, in what way could this empirical knowledge on children's competence contribute to policymaking?

The little progress achieved over the last decades in normative discussions on children's competence is dealt with in chapter 2, where we suggest a possible research agenda to make way for advancements. In chapter 3, we inventory the most adequate instruments for assessing competence.

Chapter 4 contains the research protocol of our study on children's competence assessment by a standardized tool. The results of this study are demonstrated in chapters 5 and 6, in which we describe our findings on the reliability and validity of the MacArthur Competence Assessment Tool for Clinical Research in pediatric patients of 6 to 18 years of age, and the age limits found for competence, followed by an analysis of determining factors for children's competence.

Chapter 7 examines our study on the MacArthur Competence Assessment Tool for Treatment in children and shows preliminary findings on feasibility. In chapter 8 we present a qualitative and quantitative analysis of reasons for the high rates of children's non-participation in research in order to derive strategies to optimize research participation of children.

The possible implications of the research findings for policymaking are discussed in chapter 9. The thesis concludes with a summary of the results and a reflection on future perspectives regarding research on children's decision-making competence (chapter 10).

2 Why is it hard to make progress in assessing children's decision-making competence?

Published as: Irma M. Hein, Pieter W. Troost, Alice Broersma, Martine C. de Vries, Joost G. Daams, Ramón J.L. Lindauer BMC Medical Ethics 2015, **16**:*1 doi:10.1186/1472-6939-16-1*

Abstract

Background

For decades, the discussion on children's competence to consent to medical issues has concentrated around normative concerns, with little progress in clinical practices. Decision-making competence is an important condition in the informed consent model. In pediatrics, clinicians need to strike a proper balance in order to both protect children's interests when they are not fully able to do so themselves and to respect their autonomy when they are. Children's competence to consent, however, is currently not assessed in a standardized way. Moreover, the correlation between competence to give informed consent and age in children has never been systematically investigated, nor do we know which factors exactly contribute to children's competence.

This article aims at identifying these gaps in knowledge and suggests options for dealing with the obstacles in empirical research in order to advance policies and practices regarding children's medical decision-making competence.

Discussion

Understanding children's competency is hampered by the law. Legislative regulations concerning competency are established on a strong presumption that persons older than a certain age are competent, whereas younger persons are not. Furthermore, a number of contextual factors are believed to be of influence on a child's decision-making competence: the developmental stage of children, influence of parents and peers, quality of information provision, life experience, the type of medical decision, and so on. Ostensibly,

these diverse and extensive barriers hinder any form of advancement in this conflicted area. Addressing these obstacles encourages the discussion on children's competency, in which the most prominent question concerns the lack of a clear operationalization of children's competence to consent. Empirical data are needed to substantiate the discussion.

Summary

The empirical approach offers an opportunity to give direction to the debate. Recommendations for future research include: studying a standardized assessment instrument covering all four relevant dimensions of competence (understanding, reasoning, appreciation, expressing a choice), including a study population of children covering the full age range of 7 to 18 years, improving information provision, and assessing relevant contextual data.

Background

The informed consent model assigns patients autonomy over medical interventions, including self-determination, with regard to their body, health, private life and sometimes even death. Exercising this autonomy regularly imposes a considerable burden of responsibility on the patient. However, where children and adolescents are concerned, we do not know if they are able to decide on medical issues in a meaningful way. There is no consensus on when they are competent to consent to treatment or clinical research.

Competence, as used it in this article, is the clinical concept of the ability of a person to consent to medical interventions or clinical research. Strictly speaking, incompetence denotes a legal status that in principle should be determined by a court. In clinical practice competence is generally addressed as decision-making capacity.(3) In this article we use the terms competence and decision-making capacity interchangeably, unless otherwise specified we are referring to the clinical assessment of capacity.(3) We are interested in children's competence to consent in both the treatment context and the clinical research context, although these two may not be the same.

Although laws differ between nations and states, most laws prescribe that children and adolescents, hereinafter referred to as children, can exercise their rights as a patient from a certain age, including the right to give informed consent. However, these age limits vary considerably between countries and states.

Within the context of daily pediatric practice, competence is usually assessed implicitly. However, competency can become problematic when concerns rise about the capacities of pediatric patients to make well-considered decisions. For example, in some countries, when a 12-year old boy with acute leukemia is asked to participate in a drug trial, the researcher has the authority to judge the boy competent and his decision to consent to research participation valid or invalid. Or, in the case of a 15-year old girl with anorexia nervosa who, against her parents' wishes, refuses to be tube fed, the treating pediatrician could be tasked with judging whether the girl is competent to refuse the proposed treatment. Again, this all depends on the local laws and regulations of the countries in which these cases occur.

For clinicians it is vital to strike a proper balance between protecting children's interests when they are unable to do so themselves, and respecting their autonomy when they are. Children's competence to consent, however, is currently not assessed in a standardized way. Moreover, neither the correlation between competence to give informed consent and age in children, nor which factors exactly contribute to children's competence, have ever been systematically researched.

Former discussion on children's competence to consent to medical issues has consistently been focused on normative concerns, which has impeded progress in clinical practices. The aim of this article is to offer recommendations for finding a way out of the impasse by means of identifying the gaps in knowledge about children's competence issues and by suggesting options for dealing with the obstacles in empirical research.

Discussion

Normative Aspects

History shows different perspectives on dealing with children's competence issues. The enormity of the abuse in human experimentation in World War II led to the emergence of patients' rights in medical decision-making.(6) In the ensuing years, competency issues involving children in clinical research proved especially problematic. The possibility of exposing children to the risk of harm was an ever present concern. But excluding them from research was not an option as biomedical research did prove successful: many examples showed that the mortality rate in children was drastically reduced.(6) To ensure research participation of children, while warranting their safety, specific pediatric regulations and guidelines were put in place. Nevertheless, until the nineties children kept being excluded from trials just to safeguard their vulnerability.(7) Developments regarding children's

competence in the treatment setting currently show that autonomous rights to self-determination have been extended and are now more variably assigned than before.(8)

In law, competence has traditionally been associated with age.(9) Generally the law presumes that certain persons (i.e., adults) are competent, whereas others (children) are not. The statutory age of majority is commonly set at 18 years, although there are exceptions to this rule. Normally, young children under the age of 12 have no formal right to be involved in the informed consent process with their parents.(10) Differences exist between states and countries regarding the age at which children are deemed able to make competent decisions. In Europe, domestic law determines whether or not people are competent to consent to healthcare interventions.(11) In some countries autonomous decision-making is deemed legal at age 18, while in other countries minors are allowed to take healthcare decisions from a fixed age below legal majority, e.g., 14 years in Portugal and 15 years in Denmark.(11) A more flexible system exists in most Canadian provinces and Switzerland where the competence of children to consent is evaluated on a case-by-case basis.(11) In the United States statutes often specify various minimum ages (usually 12, 14, or 16 years) for independent consent by children for specific types of treatment.(12) In the United States regulations for clinical research state that some children under the age of 18 might be able to give their assent, meaning an affirmative agreement, but the institutional review board may still waive the assent requirement.(13)

Obviously there is no international consensus on the exact age limit for presuming competence to consent in children.(14) To some extent, age limits seem arbitrary and ineffective as there are individuals above the limit who are deemed incompetent and individuals below the limit who are deemed competent. Though age limits are practicable, they may only serve their goal if they are generally in accordance. While statutory age limits have obviously taken into consideration the welfare of both society and the child, there is no clear empirical evidence regarding the competence of children's age groups.

Developmental Aspects

Elementary school children face cognitive limitations; they lack the broad-based knowledge adults possess and sometimes have trouble applying their cognitive skills to a larger problem-solving process. They may view the world in concrete terms and cannot reason maturely about abstract and hypothetical problems.(6;15) In adolescence, biological, cognitive, and social development progress and the brain undergoes substantial change with

an increase in efficiency of brain functioning. New cognitive skills are acquired, referred to by Piaget as hypothetico-deductive reasoning: the ability to think of hypothetical solutions and to formulate a systematic plan for deducing which of these solutions is correct.(15;16) Social-cognitive changes lead to increased maturity in reasoning about moral issues as well.(17) In middle adolescence (15 to 17) a strong development in metacognitive understanding emerges, including knowledge of one's own qualities, characteristics, and limitations with regard to decision-making.(18) Even with these advances, certain cognitive limitations remain, mostly involving inconsistent application of recently acquired cognitive abilities. Differences in decision-making between adolescents and adults have been found in the ability to act or think responsible, the ability to restrain impulsiveness, and the ability to place a given decision in a larger temporal context.(19) Data suggest that the adolescent brain still differs significantly from the adult brain, not least because the frontal lobes that are essential for effective executive functions mature later in children than they do in adults.(20) Adolescents generally do not fully possess the capacity to appreciate the long-term consequences of their choices until the age of 21.(20)

Apart from cognitive abilities, competence in children is thought to be related to life experience: children who have personal experiences with illness may show greater insight and understanding than children of comparable age who lack this experience.(14;21;22)

Furthermore, as children grow up they are, to a greater extent than adults, dependent on other people, especially their caretakers or parents.(15;17;23) Children may be more obedient to parents and healthcare professionals because of their need for approval or fear of rebuke from authority figures.(9;12;17;24) It is postulated that the quality of the relationship between the parent and the child and the doctor and patient is highly influential on the child's ability to make well-informed decisions.(25) An authoritative parenting style which includes direction-giving and limit-setting is positively correlated with an adolescent's developing capacity for autonomous decision-making.(20) Various authors argue that early adolescents (10 to 14) are more susceptible to peer influences than at any other age(19), which may hinder their ability to make thoughtful decisions.(18)

Empirical Data

Extensive empirical research data on children's decision-making competence are lacking. In adults, the generally accepted reference standard for competence assessment by clinicians revolves around four relevant criteria: to communicate a choice, to understand the relevant information, to appreciate

the medical consequences of the situation, and to reason about treatment choices.(26) So far, only two studies on children's competence to consent that comprised all four criteria have been conducted. Turrell and colleagues, using MacArthur Competence Assessment Tool for Treatment (MacCAT-T), conducted a comparative study on competence to consent in adolescents with anorexia nervosa and in adolescents considered healthy (in medicine known as healthy controls); that is, uncompromised by any disorders or illness, and found group differences: adolescents with anorexia nervosa tend to experience more problems in reasoning about treatment than healthy controls.(27) Koelch and colleagues examined the MacArthur Competence Assessment Tool for Clinical research (MacCAT-CR) on a small sample of children and adolescents aged 7 to 12 diagnosed with Attention Deficit Hyperactivity Disorder and concluded that the tool was feasible and offered a detailed assessment, recommending further research on the validity of the tool.(28) Other studies directed at assessing children's competence in medical decision-making vary widely; while often making use of both hypothetical and actual decision-making scenarios, these studies mostly measure only one dimension of competence, disregarding validity and reliability altogether.(24)

Practical Barriers

Some authors consider the limited application of competence assessment in research a direct result from the lack of an operationalization of children's decision-making competence.(24) Well-elaborated checklists that offer guidelines for good practice do exist;(10;22) however, the last one was written half a decade ago and systematic research data to underpin these guidelines are not available.

There is no consensus on which age spans to study, due to differences in local regulations. Decision-making situations that ask for data on children's competence may concern: complex medical situations in exceptional cases, and more routine-like medical situations in the general pediatric population. However, it is not yet established how to incorporate the varying levels of risk and complexity of the decision into the assessment. One possible way to deal with this issue, is to require a higher level of competence to consent for a decision with a higher potential risk and to require a higher level of competence to refuse for a decision with higher benefit.(22) Nevertheless, the level of risk is not yet well defined or quantifiable.(14;17)

Furthermore, it has been stated that consent to participation in research must be a more stringent process than consent to treatment, not necessarily because of higher levels of risk but because the research participants are asked to help improve general health care and thus do not profit individually.

(29) However, there are no data yet to justify the supposed differences between children's competence in the research and treatment context.

In addition, the discussion is ongoing on the dichotomous versus dimensional model of competence assessment. Buchanan and Brock(30) state that decision-making capacity is a matter of minor differences (gradual model) and competence is either present or not (threshold model). The gradual model may be more consistent with pediatric clinical practice, although a particular situation often requires a definitive assessment of competence. Some assessment instruments define decision-making capacity as the sum of different abilities, although we do not know whether these can be added up, or whether a threshold can be based on statistical arguments.(31)

Besides, children's competence relies on optimal information provision that enhances their understanding. Techniques for improving this include using clearly worded information tailored to their comprehension level. Decision-making can be facilitated by breaking the process down into smaller but linked choices. Communication difficulties can be overcome by innovative and age-appropriate techniques to convey information.(15;22) When assessing children's competence to consent, the quality and relevance of information must be optimized.

Although the need to evaluate competence to consent to treatment and clinical research has gained increasing attention, no consensus has been reached on how to assess it. The current situation has been referred to as a "hodgepodge of practices":(32) there is no gold standard and no hard empirical data.(17) In the last two decades numerous tools have been developed to assess competence in adults. To name but a few: the Competency Questionnaire, the Hopkins Competency Assessment Test, the MacCAT-T and MacCAT-CR and the Structured Interview for Competency and Assessment Testing and Ranking Inventory.(32) Of all these, the MacCAT tools have ranked the highest and are considered the best choice for measuring capacity to consent to treatment and clinical research in adults.(32) Nonetheless, assessing competence to consent in children, even with adequate tools such as the MacCAT, is still lacking. As described above, only one study confirmed feasibility of the MacCAT-CR in children(28) and MacCAT-T has only been applied in adolescents.(27)

Directions

Clinical research on children's competence to consent so far has been hampered by the absence of a guiding theory or framework with which to formulate hypotheses and interpret results. In discussions, a consensus definition of the clinical concept of children's competence may be unreachable

when taking into consideration the many questions under debate. Therefore setting out a research agenda regarding children's competence to consent has not yet been accomplished.

For professionals it might be more profitable to find an approach in empirical research than to be entangled in substantial theoretical debate with no solution in sight. In adults, systematic studies using MacCAT-CR were conducted in populations of mentally compromised patients.(33;34) Although the researchers faced comparable problems as described above, the research results contributed to further establishment of reliability and validity of a standardized competence assessment tool. Furthermore, results offered insight into the competencies of a given population regarding a given medical decision. Although the complexity of the clinical concept of children's competence implies that competence assessment methods proposed by clinical researchers should not be expected to do full justice to all legal and ethical facets, still standardized methods are indispensable and can enhance insight into the clinical concept of children's competence.

Experience from the small amount of research on children's and adults' competence to consent so far permits several recommendations for addressing the dilemmas in future research. Absent a standard, a clear definition and operationalization of children's competence is needed. For this, consulting adult literature can be a starting point. The range of abilities to be studied must include the four relevant criteria which, to our knowledge, cover the basic aspects of assessment: understanding, appreciation, reasoning and expressing a choice.(35) Previous research demonstrated that the MacCAT scales provide the best results.(32-34) Implementing such a structured multidimensional tool would make it possible to systematically assess the different dimensions of competence (4) and make outcomes comparable.(24)

Information provision should be optimized in competence assessment studies. Observational methods (video-taping or direct observation) can help us gain more insight into the decision-making process in children and identify aspects of the communication that facilitate decision-making.(24;36) Actual decision-making, instead of hypothetical decision-making, may better reflect the way children and parents behave in real-world settings. More ethnical diversity in research samples is needed in order to increase generalizability.(24)

As children's competence is likely to reflect a dynamic construct, it is important that the research design allows for these changes to be measured. The decision-making context for treatment and research is fundamentally

different in many ways, but it is not clear if research and treatment situations elicit similar or different decision-making processes. Findings from studies that examine research decisions may not be generalizable to treatment decisions and may need different assessment methods, but the situations should be compared regardless.

Next to the legal requirements for competence that emphasize cognitive components such as understanding and reasoning ability, other important contextual variables that may influence children's competence have not been very visible in research on competence so far and need more attention. The dependence of children on parents and caretakers(15;17;23) and the shift of parent orientation to peer orientation in adolescence (37) should be assessed.

The appropriate age span to be studied should cover ages at both the lower end as well as at the upper end of varying statutes and jurisdictions, leading to a study population of children from 7 to 18 years of age.

Different types of medical decisions must be studied in order to obtain data covering high risk, low risk, high complex, and low complex decisions. Although the level of risk and complexity are currently not quantifiable,(14;17) empirical research seems the most effective way to gather data and evaluate the relative contribution of these factors.

Considering that children's personal experiences with illness might enhance their competence to consent,(14;21;22;24) there is good reason to assess the duration of the illness and the experience of the child with the healthcare system.

Two studies suggested a positive relationship between intelligence and competence, as measured by the Wechsler Intelligence Scale for Children.(24) Because cognitive capacities may play an important role in decision-making competence, assessment by an intelligence test should be included.

Summary

The discussion on children's competence to consent to treatment and clinical research has made little advancement the last decade. The ongoing debate involves many normative and developmental aspects and has not yielded progress in practical implementation. The empirical approach offers an opportunity to give direction to the debate and may lead to a clear research agenda.

Recommendations for future research include: studying a standardized assessment instrument covering all four relevant dimensions of competence;

including a study population of children covering the full age range of 7 to 18 years; improving information provision; and assessing relevant contextual data. Research data are needed to underpin theories and guidelines and advance regulations concerning children's decision-making competence in the medical context.

3 Accuracy of assessment instruments for patients' competence to consent to medical treatment or research.

Published as: Hein IM, Daams J, Troost P, Lindeboom R, Lindauer RJL. Accuracy of assessment instruments for patients' competence to consent to medical treatment or research. [Protocol]. Cochrane Database of Systematic Reviews 2014, Issue 5. DOI: 10.1002/14651858.CD011099.

Abstract

Background

The informed consent model assigns patients autonomy over medical interventions and research participation. Where vulnerable patient groups including mentally comprised adults, elderly patients and children and adolescents are concerned, their degree of competence in exercising such autonomy is questionable. Therefore, the determination of patients' competence is critical in striking a proper balance between respecting the autonomy of people who are capable of making informed decisions, and protecting those whose abilities are impaired. However, clinicians may not know which standard to apply, and probably use many factors that are not formally recognized in law when assessing their patients' ability to consent to treatment or clinical research. It is not known which instruments are best qualified to assess patients' competence to consent to clinical care or research.

Objectives

To assess the reliability and validity of assessment instruments for patients' competence to consent to medical treatment or clinical research, versus a reference standard, in patients of any age with and without developmental or mental deficits, or both.

Search methods

We searched MEDLINE, EMBASE, and PsycINFO from inception to 9 July 2012. No language or publication restrictions were applied.

Selection criteria

We included all prospective diagnostic accuracy studies that assessed instruments covering the four criteria relevant for competence in most jurisdictions: to communicate a choice, to understand the relevant information, to appreciate the medical consequences of the situation, and to reason about treatment choices. Clinicians who are aware of these relevant criteria should be able to assess a patient's competence, and are used as the generally accepted reference standard. We excluded studies with a time period between index test and reference test of more than 2 weeks.

Data collection and analysis

We screened all titles generated by electronic database searches and abstracts of all potentially relevant studies were reviewed. Full papers were assessed for eligibility and data extracted by two independent assessors. Quality assessment (risk of bias and applicability) was determined using the QUADAS-2 tool.

Main results

The results of the review indicate that with current knowledge, the MacCAT-CR is the most supported instrument for assessing competence to consent to clinical research, with proved reliability and validity in populations of mentally comprised adults and older persons. For a treatment context there is no competence assessment instrument supported by reliability and validity affirmation. The MacCAT-T showed good interobserver agreement, the ACCT showed preliminary indications of good interobserver agreement and good internal consistency, but only moderate validity. Research on the remaining instruments lacked underpinning of reliability and validity.

Authors' conclusions

Our findings suggest that the MacCAT-CR has good accuracy and could be used for assessment of (in)competence in populations of mentally comprised

adults or older people in a clinical research context. In a treatment context, accuracy of competence assessment tools have not been confirmed yet, however the MacCAT-T is promising and the ACCT shows moderate results. The validity and generalizability of our findings are limited because they are based on few, heterogeneous studies with methodological flaws, with important concerns on the reference standards used. Hence, this review highlights the need to conduct more accuracy studies on competence assessment tools. Especially regarding specific populations, including children, and regarding a treatment setting, more research on assessment tools is needed.

Background

The informed consent model assigns patients autonomy over medical interventions and research participation. Where vulnerable patient groups including children and adolescents are concerned, their degree of competence in exercising such autonomy is questionable. Partly because of concerns about the adequacy of consent procedures in vulnerable populations, interest in research into decisional capacity has grown in recent years.

Consent is required for all aspects of medical care, for preventive, diagnostic or therapeutic interventions and research participation. Competence to consent, as we use it in this review, is the clinical concept of the ability of a person to consent to medical interventions or clinical research. The clinical concept of competence may be distinct from the legal one. By law clinicians are required to determine whether patients are competent to give their consent. Strictly speaking, incompetence denotes a legal status that in principle should be determined by a court. Resorting to judicial review in every case of suspected incompetence, however, would very heavily burden both the medical and legal systems; there is therefore good reason to continue the traditional practice of having clinicians determine patients' competence.(38)

Within the context of daily medical practice, competence is usually assessed implicitly. However, in some clinical settings competence regularly becomes problematic, especially when concerns arise about a person's capacity to make well-considered medical decisions. For example, if a 14-year old boy with acute lymphatic leukemia is eligible for drug trial participation, how should the researcher examine the competence of his decision to participate in the trial? If a 15-year old boy with germ cell

cancer and anemia expresses his wish not to receive blood transfusion during planned surgery, for religious reasons, is this decision a competent one? A 63-year old man with type 2 diabetes mellitus and schizophrenia is recommended a below-the-knee amputation for peripheral vascular disease but declines; how can his physician assess whether his choice is based on competent decision-making? A woman of 72, living with dementia and anemia, is recommended to undergo an investigation to trace a location of blood loss, but refuses – is she competent to give informed refusal?

The most extensive and influential research on patients' competence to consent was conducted by the MacArthur Research Network on Mental Health and the Law,(39) examining competence standards identified by the legal system as relevant to decision-making competence in the USA, UK and many other nations. The four legally-relevant abilities that were addressed were: the ability to state a choice; to understand relevant information; to appreciate the nature of one's own situation; and to reason with information. These four abilities have been generally accepted as the standard for patients' competence to consent in clinical treatment and research practice. Several interview procedures to operationalize these standards and to measure abilities have been developed in recent decades.

The determination of patients' competence is critical in striking a proper balance between respecting the autonomy of people who are capable of making informed decisions, and protecting those whose abilities are impaired. There is an undeniable need for standardized and accurate competence assessment methods.

Target condition being diagnosed

The target condition we will focus on in this review is patients' competence to consent to medical treatment or clinical research. We will cover groups of patients with and without developmental or mental deficits, or both.

Index test(s)

A variety of methods for competence assessment exist, mostly consisting of a structured or semi-structured interview format. Some instruments examine a real-life medical decision, while others are based on clinical vignettes. The instruments include the MacArthur Competence

Assessment Tool for Clinical Research (MacCAT-CR), the MacArthur Competence Assessment Tool for Treatment (MacCAT-T), and the Hopkins Competency Assessment Test (HCAT). Content, rating and cut-offs vary between index tests and there is no systematic study on their reliability and validity.

Clinical pathway

The process of obtaining informed consent starts with providing appropriate information about the proposed medical intervention and alternative options or the scientific research project. An essential element of consent is that informed choices are made voluntarily without coercion or force, and that the person is competent to make such a decision. Starting-points for competence are task and context specificity.(40) This means that competence should not be conceived as an all-or-nothing judgment implying that the patient is generally competent or generally incompetent. Instead, assessment of competence should be regarded as a specific judgment at a specific moment of whether the patient is able to complete the concrete task that they are facing.(40) The law imposes a dichotomy (competent versus incompetent) on what, from a clinical perspective, is a spectrum of capacities.(10)

In law, competence has traditionally been regarded as a function of age.(9) The statutory age of majority is generally set at 18 years, although exceptions exist in states or countries worldwide. Competence is presumed present in all adults and is rarely examined as long as the outcomes of decisions concur with the physician's recommendations.(41)

Competence to consent may be reduced by several influences such as cognitive impairment, developmental immaturity, certain psychiatric symptoms, and situational factors such as the complexity of the information. Children are deemed competent if they appear to understand information designed for their level of comprehension to an extent appropriate to the nature and scope of the decision. Internationally the statutory age limits differ for clinical research: the lower age limit varies from 7 to 15 years, while the upper age limit is set at 17 or 18 years.(42) Also, for treatment decisions various age limits exist: in some countries autonomous decision-making is lawful only from 18 years onwards, but in other countries minors are allowed to take healthcare decisions from a fixed age below legal majority starting from 12 years.(11;12) Parents decide for children who are younger than the lower age limit, as these children are considered by definition incompetent to act for themselves. For these children, no actual assessment of competence is necessary. For children between the two age limits,

informed consent is required both from children and parents, provided the child is judged competent to decide. Above the designated upper age limit, children are deemed adult in medical decision-making.

In case of incompetence in adults, usually family is allowed to make a proxy decision for general treatment decisions.(43) In the context of research, laws are less clear, but generally some kind of proxy decision-making is allowed.(43) In emergency contexts, a person's stress, pain or diminished consciousness may impair their competency. For treatment decisions the most likely result of the informed consent process under these circumstances is 'uninformed trust'.(44) Decisions on research participation in the emergency context are a matter of debate; however, formally some kind of proxy decision-making by a legally authorized person is generally allowed.(43;44)

Possibilities to advance patients' competence rely greatly on improved information provision. Decision aids are developed to provide adult patients and their families with the relevant information about the available options and possible outcomes, to support them in making a decision that is aligned with their preferences. In children decision-making can be facilitated by breaking the process down into smaller but linked choices. Communication difficulties can be overcome by innovative and age-appropriate techniques to convey information.(4) In conversation, children need clearly-worded information tailored to their comprehension level. It has been found in current practice that communication with parents and children is often flawed, and even that children are not fully informed.(4)

At present, clinicians tend to make intuitive assessments of children's and adolescents' competence, because no standardized method is available to test it objectively. Currently clinicians base their competence judgments on information such as age or school type. It is recognized that age is, at best, a proxy for developmental capacity, and that experience, maturity and psychological state are key determining factors.(4) In adults, clinicians may not know which standard to apply, and probably use many factors that are not formally recognized in law when assessing their patients' ability to consent to treatment or research.(45) In older adults and psychiatric patients, clinicians might find it difficult to distinguish between mental status examinations and competence assessment.(46) Several methods of structured competence assessment exist for adults, varying widely in procedure, reliability and validity. However, in the research context few investigators assess understanding of the research protocol and competence prior to accepting consent, and the use of standardized tools is the exception rather than the rule.(47) Data suggest that the performance of

competence assessments is often sub-optimal and hence the reliability of unstructured judgments has been poor. Providing clinicians with the generally accepted legal standards for competence improves their judgments and increases significantly the inter-rater agreement.(47) These legal standards embody the four capacities: to communicate a choice, to understand the relevant information, to appreciate the medical consequences of the situation, and to reason about treatment choices. Clinicians who are aware of these relevant criteria should be able to assess a patient's competence.(47)

Alternative test(s)

An assessment measure for competence to consent should have close conceptual relationships with the relevant standards of competence. This implies that more general measures of cognitive abilities like reading ability or Mini Mental State Examination (MMSE) would not be appropriate for a valid test of the specific context-dependent competence to consent to the research or treatment on offer.

Rationale

This review addresses the following question: which instruments are best qualified to assess patients' competence to consent to clinical care or research? We will analyze the validity and reliability of the assessment instruments.

Objectives

To assess the reliability and validity of the index tests for competence assessment versus the reference standard in people of any age. Although a gold standard for competence does not exist and the reference standard may be imperfect, we will examine whether using a structured assessment instrument instead of an expert judgment would be possible without compromising accuracy.

Secondary objectives

To examine the accuracy of standardized competence assessment instruments in the subpopulation of patients under 18 years of age, with deficits in competence due to developmental stage.

Methods

Criteria for considering studies for this review

Types of studies

We will include prospective observational studies on test accuracy. We will exclude comparative test accuracy studies, in view of the expected challenges related to the imperfect reference standard. We will also exclude diagnostic case studies.

Participants

This review deals only with assessment of competence regarding consent to treatment and consent to scientific research programs. Most assessment instruments can be applied to heterogeneous patient populations. We will include children, adolescents, adults and elderly populations with different conditions, including medical conditions, cognitive impairment, psychiatric disorders and co-morbidities. The target condition, competence to consent, can vary over time and be influenced by many factors, so the time period between index test and reference test must be short enough to be reasonably sure that the target condition did not change between the two tests.

Index tests

In an effort to standardize and hence increase the reliability and validity of competence evaluations, several formal assessment instruments have been developed. Some instruments offer a reported cut-off point. Other instruments do not provide a cut-off point, stating that a serious deficit in any of the tested domains may translate to a clinical opinion of incompetence. We anticipate variation in threshold and lack of a consensus about thresholds as challenges for this review. Data on validity and reliability of the index tests are not available in standardized summaries.

We will exclude instruments that do not cover all four relevant criteria (T for treatment context and CR for clinical research context): Aid to Capacity Evaluation (T),(48) Brief Informed Consent Test (CR),(49) California Scale of Appreciation (CR),(50) Competency Assessment Interview (T & CR),(51;52) Deaconess Informed Consent Comprehension Test (CR),(53) Direct Assessment of Decision-Making Capacity (T),(54) Evaluation to Sign Consent

(CR),(55) Hopemont Capacity Assessment Interview (T),(56-58) Hopkins Competency Assessment Test (T),(59) Informed Consent Survey (CR),(60;61) Ontario Competency Questionnaire (T),(62) Quality of Informed Consent questionnaire (CR),(63) Two-Part Consent Form (T & CR),(64) University of California San Diego Brief Assessment of Capacity to Consent (T).(65) Most vignette methods will not be included, as we judged assessment of appreciation to be insufficient.(50;66-68)

We will include the following index tests, comprising all four relevant criteria:

Assessment of Capacity to Consent to Treatment (T), a structured interview and three vignettes, studied in adults with dementia, schizophrenia and controls.(69)

Assessment of Consent Capacity for Treatment (T), three vignettes taking 45 minutes to administer and used in adults with and without mild and moderate retardation.(70)

Competency Interview Schedule (T), a structured interview, applied in people with major depression.(71)

Competency to Consent to Treatment Instrument (T), hypothetical vignettes and a structured interview, taking 20 to 25 minutes administration time. It is used in people with Alzheimer's disease, dementia, Parkinson's disease and controls.(72-75)

Competency Questionnaire (CQ), a 15-item questionnaire covering all four capacities developed by Appelbaum in 1979.(76) Each question is rated a 0 or 1, and added up for an overall score. Several modified versions were developed;

CQ – Child Psychiatric (T), a 17-item questionnaire to test competence in children to consent to psychiatric hospital care and treatment;(76) CQ-Peds (T), a 19-item questionnaire for use in pediatrics, used for inpatients and outpatients between 5 and 18 years of age;(77) and CQ-Med (T), for assessing competence of general medical patients to consent to hospitalization.(78)

MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) (CR), a semi-structured interview format developed by Appelbaum and Grisso in 2001,(3) that guides clinicians and patients through the process of information disclosure required for informed consent, combined with an assessment of the patient's capacities, in approximately 15 to 20 minutes. The instrument provides scores for each sub scale: 0 – 26 for understanding, 0 – 6 for appreciation, 0 – 8 for reasoning, and 0 – 2 for expressing a choice. MacCAT-CR is based on the structure of the MacArthur Competence Assessment Tool for Treatment (MacCAT-T).

MacArthur Competence Assessment Tool for Treatment (MacCAT-T) (T) was preceded by the original MacArthur instruments (Understanding of Treatment Disclosures, Perception of Disorder, Thinking Rationally About Treatment, Expressing a Choice). MacCAT-T was developed by Grisso and Appelbaum in 1998 and is a semi-structured interview format taking approximately 15 to 20 minutes to administer.(79) The instrument provides scores for each sub scale: 0 – 6 for understanding, 0 – 4 for appreciation, 0 – 6 for reasoning and 0 – 2 for expressing a choice. The MacCAT scales do not offer a total score or a cut-off for competence, but the scores on the sub scales need to be weighed by the interviewer. The MacCAT scales receive the most empirical support out of the variety of assessment instruments. The MacCAT scales have been tested in particular in samples of people with dementia, mental disabilities, schizophrenia and other psychiatric disorders.(80-83)

Older Adults' Capacity to Consent to Research (CR), a brief tool for assessing older adults' capacity to consent, consisting of four items each testing one of the four capacities, and used in nursing home residents and community-dwelling older adults.(84)

Structured Interview for Competency and Incompetency Assessment Testing and Ranking Inventory (T), a 20-minute structured interview examining all four aspects of competence, and used in psychiatric and medical patients.(85)

Target conditions

The target condition is the patient's competence at that moment to consent to treatment or research participation. The outcome is binary: yes or no.

Reference standards

Agreement is poor between unstructured clinical competence judgments by physicians, and no better than chance. Providing clinicians with information regarding the legal standards improves their judgments and significantly increases the inter-rater agreement to moderate (kappa 0.46).(2;86) These legal standards embody the four previously-mentioned capacities: to communicate a choice, to understand the relevant information, to appreciate the medical consequences of the situation, and to reason about treatment choices. Clinicians who are aware of these relevant criteria should be able to assess a patient's competence, and they are generally considered to establish the reference standard.(2;33;59;87) However, limitations of this

approach include the frequent discordance of expert competence judgment, which would lead to inconsistencies in the reference standard. Where the experts give their clinical judgment based on their knowledge of the four relevant criteria, the index tests consist of an operationalization of these criteria into interview questions and do not necessarily have to be administered by an expert. When agreement between reference standard and index test is high, the index test performs as well as the reference standard. Poor performance of the index test could be interpreted in different ways: it could result from imperfections in the reference standard, or the index test may not offer an accurate assessment of competence. Slightly different reference standards in each study would preclude a quantitative meta-analysis, and it would not be possible to demonstrate superiority of any of the index tests.

Search methods for identification of studies

We will use a single search strategy for this review.

Electronic searches

To identify all relevant studies, we will search the following databases: MEDLINE, EMBASE, PsycINFO. We will use the search terms and strategy summarized in Appendix 1. We will restrict the searches to human studies. We will not limit the search by language or publication status. We will perform cited reference checking of the initially included articles in Web of Science.

Data Collection And Analysis

Selection of studies

Two review authors (IH and MM) will initially screen all the titles and abstracts identified by the search strategies for eligibility. Two review authors (IH, MM and/or LG) will retrieve potentially relevant papers in full and assess them independently using a screening form developed for this review. We will list the excluded studies in the Characteristics of Excluded Studies Table. We will resolve any discrepancies by discussion. Where two review authors cannot reach agreement, we will consult the third review author. We will include study reports in English, Dutch and German; if

we find suitable studies in other languages we will attempt to get them translated. We will identify studies by the surname of the first author and the year of publication.

Data extraction and management

Two review authors (IH and LG) will independently extract a standard set of data from each study using a tailored data extraction form (see Appendix 2), resolving any discrepancies by discussion. In cases where only a subgroup of participants meet the review inclusion criteria, we will extract and present data for that particular subgroup only.

We will extract information about the capacity domains assessed.

Results of the reference test for competence to consent are dichotomous; positive is defined as 'competent' and negative as 'not competent'. Results of the index tests may be mixed: some may offer a reported cut-off point and provide dichotomous results, while others may not provide a cut-off point but report that a serious deficit in any of the tested domains translates to a clinical opinion of incompetence. In that case we will compare the various given cut-offs with the reference standard. For each comparison of index test with reference test, we will extract data on the number of true positives, true negatives, false positives and false negatives in the form of a two-by-two table.

Assessment of methodological quality

Two review authors (IH and LG) will independently assess the quality of each individual study using the checklist adapted from the QUADAS-2 tool;(88) the criteria are summarized in Appendix 3. We will answer each question on the checklist with a yes/no response, or note it as unclear if insufficient information was reported to allow us to make a judgment; we will document the reasons for this judgment. We will assess whether the study design and patient selection was appropriate, and whether the reference test and index test were rated blind to the results of each another. We will also assess if cut-off values were prespecified. Given that most instruments will not provide this information, we will not exclude studies that do not offer a prespecified cut-off but will report it as a possible risk of bias. Furthermore, we will assess whether the reference standard consisted of judgment by an expert aware of the relevant criteria, which must be accounted for by a description of the training the expert received. We will assess whether all patients received both index

test and reference test, and will exclude patient groups who did not. If an atypical reference test was used, for example competence judgment by a panel of clinicians who are not aware of the relevant criteria, we will also exclude these patient groups. We will assess the time interval between reference standard and index test; we consider two weeks as justifiable. Although in cases of acute illness the level of competency could change markedly over two weeks, we do not intend to exclude studies designed for a population of patients with chronic diseases where researchers need some time to enroll them. We will summarize the methodological quality judgments graphically.

Statistical analysis and data synthesis

We will examine the validity and reliability of the competence assessment instruments. Content validity (the degree to which the instrument's content reflects the universe of content relevant to the constructs being measured) is usually determined on the basis of expert consensus. In this review we will examine whether each instrument's construct is consistent with the widely-accepted four-capacities model.

We will assess criterion validity, the degree to which scores on a scale are associated with the standard, in terms of inter-correlations. Other useful values are the scale's sensitivity (valid positive, in this case competent) and specificity (valid negative, incompetent) rate. The accepted standard against which criterion validity is evaluated may be an established measure. In the absence of a gold standard for measuring competence, we will use the expert judgment by clinicians aware of the four relevant criteria as a reference standard.

If we have sufficient data, we will summarize results for the patient population under 18 years of age with deficits due to developmental stage only.

Marked inconsistency in the reference standards in the included studies will be particularly difficult to deal with quantitatively. In this systematic review we will demonstrate the descriptive elements of the index tests without performing a meta-analysis, which may be equally important in this first attempt at reviewing evidence on this topic.

We anticipate that within some index tests various cut-off values will have been applied to individuals. In that case we will perform the above-mentioned analyses for subgroups of studies that report similar cut-offs for that index test.

Investigations of heterogeneity

Not applicable.

Sensitivity analyses

Not applicable.

Assessment of reporting bias

We judge it acceptable not to assess reporting bias, given that very little is known about publication bias in test accuracy studies and that extrapolating from publication bias in effectiveness research may not be appropriate.

Results

Results of the search

We identified 3304 references through electronic searches of MEDLINE (Ovid SP) (N = 829), EMBASE (Ovid SP) (N = 600), and PsycINFO (Ovid SP) (N = 1875). After the exclusion of 753 duplicates, 2551 references remained; we found 2523 to be irrelevant references. Twenty-eight references on studies seemed to fulfill the inclusion criteria. We excluded seventeen studies after reading the full text. Finally, we included 11 studies and considered them for data analyses.

Included studies
Eleven studies are included, of which four studied participants' competence to consent to clinical research(33;34;84;89) and 7 studied participants' competence to consent to treatment.(69;71;78;85;90;91) Six studies reported on MacCAT scales,(33;34;81;89-91) other assessment instruments were reported on in one study each: Competency Interview Schedule (CIS),(71) Competency Questionnaire-Med (CQ-Med),(78) Older Adults' Capacity to Consent to Research (OACCR),(84) Assessment of Capacity to Consent to Treatment (ACCT),(69) and Structured Interview for Competency and Incompetency Assessment Testing and Ranking Inventory (SICIATRI).(85) Five studies reported on competence to consent in a geriatric population,(33;78;84;90;91) four studies in a population of patients with psychiatric

disorders,(34;71;81;89) and two studies in a mixed population (geriatric/psychiatric,(69) psychiatric/medical conditions(85)). There were no studies in a population of minors.

Excluded studies

Seventeen studies are excluded from the review. The reasons for exclusion were: the index test did not cover all four relevant criteria for competence in ten studies (Hopkins Competency Assessment Test,(59;92-94) Competency Questionnaire,(95) University of California San Diego Brief Assessment of Capacity to Consent,(65;96) Hopemont Capacity Assessment Interview,(57) and vignette methods).(67;68) Four studies did not use a reference standard.(28;77;97;98) Two studies used an invalid reference standard (a Community Treatment Order,(99) and competence judgments of untrained clinical teams).(100)

Methodological quality of included studies

Overall, concerns were high on risk of bias and applicability of the reference tests used in the included studies (Figure 1). Only two studies were considered to be of good quality,(33;34) and one study to be of moderate quality.(78) The other included studies raised high or unclear concerns on at least two out of three quality dimensions concerning patient selection, reference standard and index test (Figure 2).

Figure 1. Risk of bias and applicability concerns graph: review authors' judgments about each domain presented as percentages across included studies

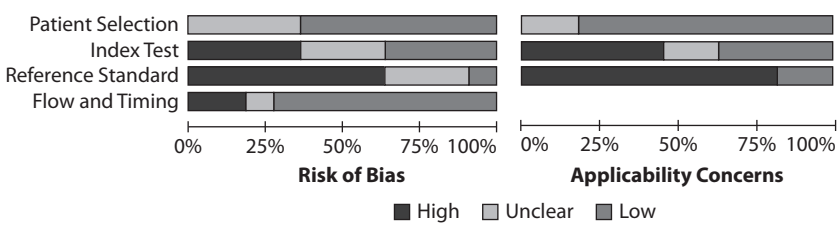
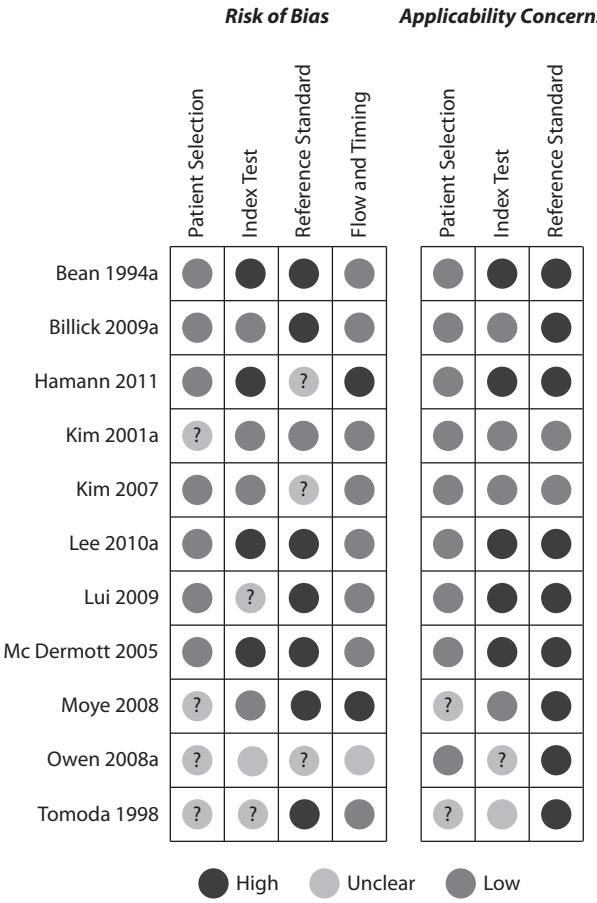


Figure 2. Risk of bias and applicability concerns summary: review authors' judgments about each domain for each included study



Findings

Accuracy of assessment tools

All disagreements between evaluators were resolved through discussion. The data extraction was difficult mainly because of the above mentioned heterogeneity in the definition of the reference standard. Very few studies used the preset reference standard being competence judgment by clinicians who are aware of and trained in assessing the four domains of competence (to communicate a choice, to understand the relevant information, to appreciate the medical consequences of the situation, and to reason about

treatment choices). Data of only two studies of good quality on MacCAT-CR could be combined,(33;34) and outcomes of one study on CQ-Med can be presented as reliable.(78) Eight studies show shortcomings concerning suitability for establishing accuracy, and will be presented and discussed separately. The results are presented according to the index test used.

Index test 1: MacCAT-CR

There were two studies of good quality using MacCAT-CR. In the first study, participants were 37 patients with Alzheimer's disease and 15 elderly controls.(33) The gold standard was based on expert judgments on competence to consent of the patients with Alzheimer's disease. Results show a high interrater reliability of the MacCAT-CR, ICC=0.94. Optimal cutoffs for the sub scale scores of the MacCAT-CR were determined based on the reference standard: understanding 18 (sensitivity=90%, specificity=88%); appreciation 5 (sensitivity=80%, specificity=100%); and reasoning 6 (sensitivity=100%, specificity=75%). Using this cutoff, 31 of the 37 patients with Alzheimer's disease were found incompetent and all 15 comparison subjects found competent. These results suggest accurate cutoff scores on sub scales of the MacCAT-CR.

The second study, performed by the same first author, examined competence to consent in 91 people with severe mental illness (55 participants in a schizophrenia study, and 36 people recruited at in- and outpatient clinics serving people with severe and persistent mental illness) and 40 people in the community comparison group.(34) The reference standard was established by three psychiatrists with experience in assessing decisional capacity. These experts gave their categorical judgment (competent/incompetent) based on video-taped MacCAT-CR interviews with the participants. A majority (2 or 3 out of 3) agreement among the three experts was used to determine the final competence status. The reference standard was established for 90 people with severe mental illness and for 11 controls. A disadvantage of this approach is that the expert judgment was influenced by the information from the MacCAT-CR interview. Results demonstrate that 25 of the 101 people judged, were deemed incompetent. Pairwise kappa coefficients among the experts establishing the reference standard ranged from 0.56 to 0.90, the group kappa coefficient was 0.69. Intra-class correlations for total scores of MacCAT-CR subscales were 0.93 for understanding, 0.89 for appreciation, 0.84 for reasoning. MacCAT-CR sub-scale scores were analyzed for determining the optimal cutoff with the highest sensitivity and specificity. The area under the ROC curve was higher for understanding, 0.94,

than for appreciation, 0.85, and reasoning, 0.80. For understanding, the optimal cutoff corresponded with a score of 18. This is the second study indicating that an accurate cutoff on a subscale of the MacCAT-CR, in this case understanding, can be determined.

One study on MacCAT-CR did not meet the quality criteria for the index test and reference test,(89) taking into account that the reference standard consisted of the clinical judgment of competence by the Principal Investigator, and the index test MacCAT-CR was interpreted with knowledge of the reference standard. Results are hard to interpret because of the deficient quality of the measures. The study population consisted of 106 forensic psychiatric patients, and results showed that psychiatric symptoms were modestly related to decision-making competence.

Index test 2: CQ-Med

The study on the CQ-Med is considered to be of sufficient quality.(78) The study population consisted of 29 older patients admitted to a geriatric medicine unit, who were assessed on their competence to consent to hospitalization and treatment. The CQ was developed by Appelbaum in 1981 and was further modified into the CQ-Med by the research group of Billick and colleagues, for assessing the competence of general medical patients to consent to hospitalization. The reference standard consisted of a competence assessment using a clinical exam by a geriatric psychiatry fellow. Results show that the reference standard correlated with the CQ-Med, r=0.58. Validation of the CQ-Med to the reference standard showed a sensitivity of 0.80 (8/10) and a specificity of 0.60 (3/5). Reported limitations of the study include the small sample size and the lack of comparison of the CQ-Med with other competence assessment instruments, such as the MacCAT-T developed by Appelbaum in 1997. Concerns rise on covering all four capacities by the CQ-Med, as the study does not describe exactly how the CQ-Med is composed. The original CQ was left out of analysis because we judged that the emphasis was on understanding, CQ-Med may struggle with the same issue.

Index test 3: MacCAT-T

One study on MacCAT-T was a cross-sectional survey conducted in a sample of patients with mild cognitive impairment and mild dementia. (90) One-hundred patients were included, their relatives (99) and their referring physicians. Decision-making capacity concerning a hypothetical medical decision was examined, making use of the MacCAT-T as index test and referring physician's judgment on patient's medical decision-making

competence as a reference standard. Some sections of the MacCAT-T were not included because patients had different diagnoses and the treatment was hypothetical. Results demonstrated that physician's confidence in patient's decision-making correlated significantly with the MacCAT-T sub scale understanding, correlation coefficient, 0.24, and appreciation of treatment, 0.34. Physician's confidence in patient's decision-making did not correlate with the sub scales reasoning, 0.14, and expressing a choice, 0.10. Both the reference standard as the index test, however, do not fulfill all the quality requirements.

Lui(91) studied competence to make treatment decisions in 66 community dwelling Chinese older people, of whom 33 with very mild dementia and mild Alzheimer disease, using MacCAT-T as an index test. The reference standard used was a competence judgment by three psychiatrists based on four audio taped questions. Results show that 17 of the 33 patients were judged incompetent on the reference standard, and 15 on MacCAT-T. Participants who were incompetent on the reference standard, scored significantly lower on the MacCAT-T sub scales. The authors describe that the MacCAT-T scores correlate significantly with the competence judgment of a clinician based on that same MacCAT-T interview, which however obviously must be influenced by it. Interrater agreement of MacCAT-T among three raters was good: 0.83 for understanding, 0.78 for appreciation, 0.77 for reasoning, and 0.64 for expressing a choice.

The MacCAT-T was studied in a large sample of 350 psychiatric patients referred for admission and treatment.(81) There was not a clear reference standard, as the study aimed at estimating the prevalence of mental competence to make treatment decisions in people from different diagnostic and legal groups admitted to psychiatric hospital. The study compared the opinion of the psychiatric trainee with the outcome of the MacCAT-T, however, the study population was partly assessed by trainees (n=138) and partly assessed by MacCAT-T (n=200). The prevalence of incompetence was estimated to be 60% (95% CI 55-65).

Index test 4: ACCT

Moye and colleagues(69) studied the ACCT in 59 adult participants: 20 people with dementia, 20 with schizophrenia, and 19 controls from a primary care clinic. The ACCT is developed by Moye and starts with a value interview, followed by 3 hypothetical vignettes. The reference standard consisted in 27 cases of the rating based on the clinical opinion of the primary care provider, and in 12 cases of the retrospective rating by three experienced clinicians not trained in the four relevant criteria. Internal consistency

reliability was alpha=0.96 based on all items in 56 participants, and for sub scale understanding a=0.91, appreciation, a=0.88, reasoning, a=0.82, and communicating a choice, a=0.66. For 10 cases, interobserver agreement was analyzed for the total score, r=0.90, and for sub scale understanding, r=0.90, appreciation, r=0.89, reasoning, r=0.68, and communicating a choice, r=0.98. Validity of the ACCT based on the reference standard of primary care providers' judgment, showed kappa=0.44. Validity of the ACCT based on the reference standard of experienced clinicians' judgment, showed kappa=0.50.

Index test 5: OACCR
OACCR is a four-item instrument for assessing competence to consent to clinical research developed and studied by Lee and colleagues in 203 nursing home residents and 201 community dwelling older adults in South Korea.(84) The reference standard consisted of a competence judgment by the capacity to consent screen, a 10-item instrument covering all four relevant criteria. Internal reliability of OACCR was demonstrated with high item-total correlations, ranging form 0.59 to 0.76 and an overall reliability coefficient of 0.85. Interobserver agreement is not reported. To establish validity, the relationship between the OACCR and the capacity to consent screen was analyzed using Pearson correlation coefficient, r=0.94. In 401 participants cross-tab analysis showed sensitivity of 99% and specificity of 73%.

Index test 6: CIS
The CIS consists of 15 items: 4 on evidencing a choice, 3 on understanding information, 2 on rational reasoning and 5 on appreciation.(71) Responses are rated on a 7 point Likert scale: 1-3 adequate, 4 marginal, 5-7 inadequate. The outcomes of competence on the CIS are not reported. The reference standard was based on judgment by a third person who reviewed medical records to determine whether the patient was found competent or incompetent by the attending physician. Participants were 96 admitted patients with severe psychiatric disorders referred for electroconvulsive therapy. Results describe that 75 patients were found competent on the reference standard. In 13 patients, test-retest reliability was analyzed for the average correlations based upon pooled items: intra class, r=0.79. In 11 patients, interrater reliability was examined, intra class correlation coefficient for the average correlations based upon pooled items was r=0.95. Internal consistency of the instrument was examined using inter-item correlation coefficients, which ranged from 0.39 to 0.85. Validity

was tested by calculating correlations of individual item scores with the reference standard, which ranged from 0.35 to 0.73, showing a significant association. Further analysis of sensitivity, specificity or predictive value was not performed.

Index test 7: SICIATRI
Competence to consent to treatment was tested using SICIATRI in 48 inpatients, of which 25 had a psychiatric disorder and 23 a medical condition. (85) The SICIATRI consists of 12 items, each rated on a 3-point scale, after administration the patient was classified into 5 categories ranging from completely incompetent to completely competent. The reference standard consisted of a competence rating by the attending physician using the Disclosure Consent Checklist, which focuses on understanding the nature and purpose of hospitalization and treatment. Interrater reliability of the SICIATRI is expressed by kappa's ranging form 0.14 to 0.82, with 6 out of 12 items showing a kappa of 60 or higher. On the reference standard, 13% of the participants were incompetent. Thirty-five (73%) patients were competent on both reference standard and SICIATRI, in cross-tab analysis two cells have numbers under 5. A total agreement of competence classification between SICIATRI and reference standard was 81.3%. Sensitivity of the SICIATRI was 0.83 and specificity 0.67.

Discussion

Our review demonstrated that there are few reported studies on competence assessment tools that fulfill the criteria of solid diagnostic test accuracy studies. Considering that competency issues are relatively frequent in clinical practice with mentally comprised patients, it is surprising that we found only three studies with analyzable data of sufficient quality. (33;34;78)

Feasibility
Feasibility was not a problem for most instruments under study. Feasibility of MacCAT-CR, (33;34) MacCAT-T,(81;90;91) ACCT,(69) OACCR,(84) and CIS(71) is established. Doubts rise on feasibility of CQ-Med(78) because of concerns regarding the coverage of all four domains relevant for competent decision-making, therefore CQ-Med will not be considered for recommendation until these doubts can be dissolved.

Reliability

Overall, the included studies lacked in reporting on internal consistency of the instruments, and only 3 studies showed that the instrument met the standard. Good interobserver agreement was demonstrated for MacCAT-CR and MacCAT-T only.

Internal consistency
The studies on MacCAT-T, CQ-Med, and SICIATRI did not report on internal consistency of the scale. MacCAT-CR,(34) OACCR,(84) and ACCT(69) showed good internal consistency. For CIS, inter-item correlation coefficients ranged from low to good.(71)

Interobserver agreement
The studies on MacCAT-CR by Kim and colleagues reported good interobserver agreement in a sample of sufficient participants.(33;34) Interobserver agreement of MacCAT-T was described by Lui and colleagues to be good.(91) For the CIS, good interobserver agreement was reported for a small sample, consisting of 11 participants, which can be considered a preliminary indication.(71) SICIATRI showed a wide range in interobserver reliability between the items, which renders the interobserver reliability for the total scale with some weaknesses.(85) For ACCT good interobserver agreement was reported in a small sample of 10 patients,(69) also forming a preliminary indication of interobserver reliability. No reports on interobserver agreement were found for CQ-Med(78) and OACCR.(84)

Validity

The only two studies that met the quality criteria for feasibility, index test and reference standard, study the MacCAT-CR. The studies by Kim validated the MacCAT-CR scale against an expert judgment standard.(33;34) Depending on the prevalence of incompetence in the studied population, these studies allow for estimation of optimal cutoffs of the subscale scores. Both studies report on un optimal cutoff for subscale understanding of 18 points. The studies explain how positive predictive value (PPV, the probability that a person performing below the cutoff score is indeed incompetent) and negative predictive value (NPV, the probability that a person performing above the cutoff is in fact competent) depend on the prevalence of (in) competence in the given population (e.g. use of a high cutoff score when prevalence of incompetence is low, would lead to excluding many persons

unjustly as incompetent). Therefore the authors suggest that for establishing optimal cutoff scores, knowledge of prevalence of (in)competence must be incorporated. The validity of a cutoff on a MacCAT-CR subscale is demonstrated.

The other studies do not comply with the requirements. Studies on MacCAT-T do not offer data for estimating validity: either data are lacking,(81;90) or the reference standard is insufficient for analysis.(91) The ACCT demonstrated moderate correlation with the reference standard, although the reference standard was of insufficient quality.(69) The OACCR showed good construct validity, however the reference standard demonstrated similarities with the index test and therefore the high correlation coefficient may present an overestimation. For the CIS only associations between reference standard and index test were demonstrated, but no further relevant measures of validity, which does not allow for establishing validity.(71) The study on SICIATRI reported high sensitivity and adequate specificity, however cross-tab analysis shows insufficient distribution amongst the cells.(85)

Summary of Main Results

In this review, 11 studies on instruments for assessing competence to consent to treatment or clinical research were included, all concerning the adult or older population, together reporting on 7 different instruments. Overall, quality of the studies under review raised many concerns, mostly regarding insufficient quality of the reference standard. Initially, three studies were considered of sufficient quality. Closer review of the studies revealed that CQ-Med produced doubts on feasibility, leaving two studies of sufficient quality, both on MacCAT-CR.

The results of the review indicate that with current knowledge, the MacCAT-CR is the most supported instrument for assessing competence to consent to clinical research, with proved reliability and validity in populations of mentally comprised adults and older persons. The OACCR, also applicable in a research setting, lacks this underpinning. For a treatment context there is no competence assessment instrument supported by reliability and validity affirmation. The MacCAT-T showed good interobserver agreement, the ACCT showed preliminary indications of good interobserver agreement and good internal consistency, but only moderate validity. Results of research on the CIS and the SICIATRI renders little support for these instruments until now. Taking into account the similarities between the MacCAT-T and the MacCAT-CR, use of the MacCAT-T may be supported by the positive accuracy outcomes of the MacCAT-CR.

Strengths and weaknesses of the review

Despite an extensive and thorough search, we retrieved only 11 studies with varying sample sizes, of which 7 were assessed with considerable risk of bias due to sub-optimal study design. In the end only 2 studies assessed a competence assessment tool on reliability and validity. No study assessed competence to consent in children.

Applicability of findings to the review question

The accuracy of instruments for assessing patients' competence to consent could be addressed regarding a clinical research context, in populations of mentally compromised adults and older people. For a treatment context, results are less outspoken, however a recommendation for an instrument that will frequently be applicable is possible. In settings with lower prevalence of the target condition, validity of cutoffs must be estimated beforehand. The applicability to other specific participant groups, e.g. children, is even more uncertain.

Authors' Conclusions

Implications for practice

The accuracy of competence assessment instruments partly depends on the prevalence of (in)competence in the study population. Our findings suggest that the MacCAT-CR has good diagnostic accuracy and could be used for assessment of (in)competence in populations of mentally compromised adults or older people in a clinical research context. In a treatment context, accuracy of competence assessment tools have not been confirmed yet, however the MacCAT-T is most promising and ACCT shows preliminary indications for reliability but moderate validity. The validity and generalizability of our findings are limited because they are based on few, heterogeneous studies with methodological flaws, with important concerns on the reference standards used.

Implications for research

Accuracy of assessment studies on patients' competence to consent may be difficult, because a systematic study design requires establishing a firm

reference standard. Hence, this review highlights the need to conduct more accuracy studies on competence assessment tools. Especially regarding specific populations, including children, and regarding a treatment setting, more research on assessment tools is needed.

Appendix 1 Search Strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Search Date: 9 July 2012:

1. informed consent.ab,sh,ti.
2. (decision* adj3 capacit*).ab,ti.
3. (capacit* adj3 consent).ab,ti.
4. disclosed information.ab,ti.
5. (information adj3 reasoning).ab,ti.
6. (express* adj3 choice).ab,ti.
7. consent form?.ab,ti.
8. mental capacity.ab,sh,ti.
9. mental competen*.ab,ti.
10. mental competency/
11. mental incompeten*.ab,ti.
12. patient participation.ab,sh,ti.
13. or/1-12 [competence to consent]
14. decision making/ or decision making.ab,ti.
15. consensus/ or consensus.ab,ti.
16. or/13-15 [competence to consent sensitive]
17. (macarthur adj3 tool).ab,ti.
18. maccat.ab,ti.
19. consent questionnaire.ab,ti.
20. deaconess informed.ab,ti.
21. two part consent.ab,ti.
22. (california adj3 appreciation).ab,ti.
23. vignette method?.ab,ti.
24. informed consent survey.ab,ti.
25. competency interview schedule.ab,ti.
26. assessment of consent capacity for treatment.ab,ti.
27. Hopemont capacity assessment interview.ab,ti.
28. aid to capacity evaluation.ab,ti.

29. direct assessment of decision making capacity.ab,ti.
30. cq peds.ab,ti.
31. competency questionnaire.ab,ti.
32. SICIATRI.ab,ti.
33. structured interview for competenc*.ab,ti.
34. (hopkins adj2 assessment).ab,ti.
35. brief informed consent.ab,ti.
36. or/17-35 [all relevant psychological tests]
37. (psychiatric adj3 scale?).ab,ti.
38. (psychiatric adj3 test?).ab,ti.
39. (psychologic* adj3 scale?).ab,ti.
40. (psychologic* adj3 test?).ab,ti.
41. (neuropsycholog* adj3 test?).ab,ti.
42. (neuropsycholog* adj3 scale?).ab,ti.
43. (neuropsychiatric adj3 test?).ab,ti.
44. (neuropsychiatric adj3 scale?).ab,ti.
45. psychological tests/ or exp aptitude tests/ or language tests/ or exp neuropsychological tests/
    or exp personality tests/
46. exp Psychiatric Status Rating Scales/
47. or/37-46 [psychological tests general]
48. 36 or 47 [psychological tests sensitive]
49. 16 and 48

OVIDSP PsycINFO, 1806 to Present
Search Date: 11 July 2012

1. (macarthur adj3 tool).ab,id,ti,tm.
2. maccat.ab,id,ti,tm.
3. consent questionnaire.ab,id,ti,tm.
4. deaconess informed.ab,id,ti,tm.
5. two part consent.ab,id,ti,tm.
6. (california adj3 appreciation).ab,id,ti,tm.
7. vignette method?.ab,id,ti,tm.
8. informed consent survey.ab,id,ti,tm.
9. competency interview schedule.ab,id,ti,tm.
10. assessment of consent capacity for treatment.ab,id,ti,tm.
11. Hopemont capacity assessment interview.ab,id,ti,tm.
12. aid to capacity evaluation.ab,id,ti,tm.
13. cq peds.ab,id,ti,tm.

14. competency questionnaire.ab,id,ti,tm.
15. SICIATRI.ab,id,ti,tm.
16. structured interview for competenc*.ab,id,ti,tm.
17. (hopkins adj2 assessment).ab,id,ti,tm.
18. brief informed consent.ab,id,ti,tm.
19. (competency adj3 interview).ab,id,ti,tm.
20. (Hopemont adj4 interview).ab,id,ti,tm.
21. or/1-20 [specific psych. tests]
22. ("2220" or "2222" or "2223" or "2224" or "2225" or "2226").cc.
23. exp testing/
24. 22 or 23 [psych. tests / testing]
25. decision making.ab,id,sh,ti.
26. informed consent.ab,id,sh,ti.
27. voluntary consent.ab,id,ti.
28. (decision* adj1 capacit*).ab,id,ti.
29. or/25-28 [informed consent specific]
30. 24 and 29
31. ("3400" or "3410" or "3430" or "3450" or "3470").cc.
32. 30 not 31
33. 21 or 32
34. limit 33 to ("0100 journal" or "0110 peer-reviewed journal" or "0400 dissertation abstract")

OVIDSP Embase, 1947 to Present
Search Date: 9 July 2012

1. informed consent.ab,sh,ti.
2. (decision* adj3 capacit*).ab,ti.
3. (capacit* adj3 consent).ab,ti.
4. disclosed information.ab,ti.
5. (information adj3 reasoning).ab,ti.
6. (express* adj3 choice).ab,ti.
7. consent form?.ab,ti.
8. mental capacity.ab,sh,ti.
9. mental competen*.ab,ti.
10. mental incompeten*.ab,ti.
11. patient participation.ab,sh,ti.
12. or/1-11 [competence to consent]
13. decision making/ or decision making.ab,ti.
14. consensus/ or consensus.ab,ti.

15. or/12-14 [competence to consent sensitive]
16. (macarthur adj3 tool).ab,ti.
17. maccat.ab,ti.
18. consent questionnaire.ab,ti.
19. deaconess informed.ab,ti.
20. two part consent.ab,ti.
21. (california adj3 appreciation).ab,ti.
22. vignette method?.ab,ti.
23. informed consent survey.ab,ti.
24. competency interview schedule.ab,ti.
25. assessment of consent capacity for treatment.ab,ti.
26. Hopemont capacity assessment interview.ab,ti.
27. aid to capacity evaluation.ab,ti.
28. direct assessment of decision making capacity.ab,ti.
29. cq peds.ab,ti.
30. competency questionnaire.ab,ti.
31. SICIATRI.ab,ti.
32. structured interview for competenc*.ab,ti.
33. (hopkins adj2 assessment).ab,ti.
34. or/16-33 [all relevant psychological tests]
35. psychometric?.ab,ti.
36. psychometry.ab,sh,ti.
37. (psychiatric adj3 scale?).ab,ti.
38. (psychiatric adj3 test?).ab,ti.
39. (psychologic* adj3 scale?).ab,ti.
40. (psychologic* adj3 test?).ab,ti.
41. (neuropsycholog* adj3 test?).ab,ti.
42. (neuropsycholog* adj3 scale?).ab,ti.
43. (neuropsychiatric adj3 test?).ab,ti.
44. (neuropsychiatric adj3 scale?).ab,ti.
45. neuropsychological test/
46. psychological rating scale/
47. or/35-46 [psych. tests sensitive]
48. 15 and 47
49. or/37-46
50. 15 and 49
51. 50 not 34
52. 34 or 50

Appendix 2 Data Extraction Form

Study ID	First author, year of publication
Clinical features and settings	Presenting conditions, clinical setting
Participants	Sample size, age, sex, ethnicity, country.
Study design	Were patients enrolled retrospectively or prospectively? Was the sampling method consecutive or random? Duration between reference test and index test.
Target condition	Competence to consent to treatment or research participation.
Reference standard	The reference standard test(s) used
Index tests	The index test used. Details of the test content, operators, including any special training provided. Cut-off point used.
Results	Number of true positives, true negatives, false positives, false negatives
Notes	Source of funding.

Appendix 3 Quality Assessment Form

1. Patient selection

A. Risk of bias

Was a consecutive or random sample of patients enrolled? Yes/No/Unclear

Was a case control-design avoided? Yes/No/Unclear

Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias?

Risk: high/low/unclear

B. Concerns regarding applicability

Is there a concern that the included patients (prior testing, presentation, intended use of index test and setting) do not match the review question?

Concern: high/low/unclear

2. Index test(s)

A. Risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear

If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias?
Risk: high/low/unclear

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?
Concern: high/low/unclear

3. Reference standard

A. Risk of bias

Is the reference standard likely to correctly classify the target condition?
Yes/No/Unclear

Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?
Risk: high/low/unclear

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?
Concern: high/low/unclear

4. Flow and timing

A. Risk of bias

Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear

Did all patients receive a reference standard? Yes/No/Unclear

Did patients receive the same reference standard? Yes/No/Unclear

Were all patients included in the analysis? Yes/No/Unclear

Could the patient flow have introduced bias?
Risk: high/low/unclear

4 Assessing children's competence to consent to research by a standardized tool: a validity study

Published as: Hein IM, Troost PW, Lindeboom R, de Vries MC, Zwaan CM, Lindauer RJ. Assessing children's competence to consent in research by a standardized tool: a validity study. BMC Pediatr 2012;12:156

Abstract

Background

Currently over 50% of drugs prescribed to children have not been evaluated properly for use in their age group. One key reason why children have been excluded from clinical trials is that they are not considered able to exercise meaningful autonomy over the decision to participate. Dutch law states that competence to consent can be presumed present at the age of 12 and above; however, in pediatric practice children's competence is not that clearly presented and the transition from assent to active consent is gradual. A gold standard for competence assessment in children does not exist. In this article we describe a study protocol on the development of a standardized tool for assessing competence to consent in research in children and adolescents.

Methods/design

In this study we modified the MacCAT-CR, the best evaluated competence assessment tool for adults, for use in children and adolescents. We will administer the tool prospectively to a cohort of pediatric patients from 6 to18 years during the selection stages of ongoing clinical trials. The outcomes of the MacCAT-CR interviews will be compared to a reference standard, established by the judgments of clinical investigators, and an expert panel consisting of child psychiatrists, child psychologists and medical ethicists. The reliability, criterion-related validity and reproducibility of the tool will be determined. As MacCAT-CR is a multi-item scale consisting of 13 items, power was justified at 130–190 subjects, providing a minimum of

10–15 observations per item. MacCAT-CR outcomes will be correlated with age, life experience, IQ, ethnicity, socio-economic status and competence judgment of the parent(s). It is anticipated that 160 participants will be recruited over 2 years to complete enrollment.

Discussion

A validity study on an assessment tool of competence to consent is strongly needed in research practice, particularly in the child and adolescent population. In this study we will establish a reference standard of children's competence to consent, combined with validation of an assessment instrument. Results can facilitate responsible involvement of children in clinical trials by further development of guidelines, health-care policies and legal policies.

Introduction

Currently over 50% of drugs prescribed to children have not been properly evaluated for safety and efficacy in their age group. One key reason why children have been excluded from clinical trials is that they are not considered capable of understanding research information. This means that they are not considered able to exercise meaningful autonomy over the decision on trial participation. By Dutch law, competence to consent in children is presumed to be present at the age of 12 and above. In pediatric clinical practice, though, children's competence is not that clearly presented. Children may express an increasing degree of competence over time as their abilities are developing, so there is a gradual transition from assent to the more active consent.

If we knew which children were competent to consent and which were not, it would be possible to involve them in the decision-making process about clinical trial participation in a conforming way. Non-competent children would no longer have to be burdened by the full informed-consent procedure, while competent children would be more actively engaged in that procedure, with extra weight given to their opinions. This would facilitate the implementation of clinical trials in children and adolescents and still protect the vulnerable subjects.

Previous studies show that children's competence has never been systematically examined in a standardized manner.(24) The aim of this study is to develop a standardized competence assessment tool for children and to investigate the correlation between competence and age, IQ and

patient characteristics. Once an objective tool for competence assessment becomes available, it can be implemented in inclusion stages of clinical trials in children.

This prospective observational study seeks to examine whether children's competence to consent to research can be assessed in a reliable and valid way by means of a clinical tool.

Background

Nature of competence

Individuals are competent if they are able to make decisions based on understanding and on rational reasons.(1) Competent decisions represent informed, free, self-determined choices and should be respected. This applies to informed consent as well as to informed refusal. Competence is task- and context-specific, which means that assessment of competence should be regarded as a specific judgment at a specific moment of the ability of the patient to fulfill the concrete task that he is facing.(1) Legal competence in health care requires being able to communicate a choice, understanding information one is given, appreciation of one's circumstances and mental capacities to reason and deliberate.(30;101)

Legislation

In current pediatric practice, parents and children undergo an informed consent procedure. According to the Dutch Medical Treatment Contracts Act (WGBO), which applies to treatment situations, parents decide for their children younger than 12 years of age, who are considered by definition incompetent to act for themselves. For these children, no actual assessment of competence is necessary. For children aged 12 to 15, informed consent is required both from children and parents, provided the children are judged competent to decide. From 16 years of age, children are deemed adult in medical decision making. In the Dutch Medical Research Involving Human Subjects Act (*Wet Medisch-wetenschappelijk Onderzoek met Mensen*, WMO), the same arrangements apply but age limits are set at 12 and 18 years of age. Children are deemed competent if they appear to understand information designed for their level of comprehension to an extent appropriate to the nature and scope of the decision. Internationally, the statutory age limits differ for clinical research: the lower age limit varies form 7 to 15, the upper age limit is set at 17 or 18 years.(102)

In the Netherlands, the Doek Committee was installed to advise the State Secretary of Health, Well-being and Sports and the Minister

of Justice(103) on the desirability of adapting the current regulations for medical scientific research with minors that does not benefit them directly. They concluded that the protection criteria in the Medical Research Involving Human Subjects Act give children little room to make decisions based on their own ideas and values. Children under 12 who wish to refuse participation in clinical research can formally only make that known through resistance. Children older than 12 may withhold permission, but if they do decide to participate, that can formally be nullified by their parents' refusal. This conflicts with the prevailing view that children have the right to make decisions consistent with their value systems and life view. Children may be seen as moral agents, possessing autonomy.(104) The Doek Committee therefore recommends that the will (the assent or refusal) of a younger child be taken into account to the degree that the child can understand the issues. The Task-force in Europe for Drug Development for the Young(105) issued recommendations to be implemented Europe-wide, stating, amongst other things, that minors should be involved in the informed-consent process in proportion to age and degree of maturity. By assessing competence to consent in children and adolescents more objectively than is now the case, greater justice could be done to the ideal of respect for the developing autonomy of children in decision making, in accordance with national and international recommendations.

Competence assessment in current pediatric practice

At present, clinical investigators are able to make only intuitive assessments of children's competence, because no standardized method is available to test it more objectively. Conceivably, the age standards prescribed by law may have too much influence on that intuitive decision by the assessor. Research evidence indicates that children under 12 may also be capable of making well-considered decisions(23;106) and that children as young as 9 can understand the issues involved in clinical trials.(23) This suggests a mismatch between children's developmental level of decision-making maturity and the age limits set by legislation. The assessment of competence is subject to two pitfalls: complex research decisions may be imposed on children who are unable to make them, while capable children who want to take part may be inadvertently excluded.(106) It is recognized that age is, at best, a proxy for developmental capacity, and that experience, maturity and psychological state are key determining factors. This means that children's competency to make important decisions ought to be assessed more individually than is presently the case.

A recent study has shown that doctors and researchers tend to judge a child as competent if the child's decision conforms to their own ideas of the child's best interest.(107;108) That means that competence is gauged by the content of the decision rather than by the *process of reasoning* in deciding about participation. It is therefore vital for clinical researchers to get access to a standardized, objective method to aid them in the informed-consent procedure, and thus improve the rigor of their judgment of children's competence to consent.

Assessment of competence by MacCAT-CR

Until recently, literature on children's competence assessment was limited. Two reviews summarize the empirical literature on children's competence to consent in research and treatment settings.(23;24) A variety of different definitions and measures emerge from studies on children's competence. Two quantitative instruments, namely the Competency Questionnaire – Child Psychiatric (CQ-ChP)(76) and the Hopkins Competency test (HCAT),(109) were examined, and some other authors used semi-structured interviews. Only Weithorn's interview examined all four sub-domains of competence (see below).(110)

Empirical studies on adults have resulted in a variety of operational translations of the concept of competence into assessment instruments. Dunn(32) assessed 23 existing instruments in terms of format, content, features of administration and psychometric properties and concluded that the MacArthur Competence Assessment Tools for Clinical Research (MacCAT-CR) and for Treatment (MacCAT-T) receive the most empirical support. These instruments have been tested in particular in samples of people with dementia, mental disabilities, schizophrenia and other psychiatric disorders. There are initial indications of validity(35) and a high degree of reliability.(80)

The MacCAT-CR is a semi-structured interview format that helps clinical investigators to assess research candidates' competence to give informed consent to participation in trials. It measures the four aspects of decision-making capability that reflect the standards for competence to consent in most jurisdictions: (1) *understanding* the disclosed information about the nature of the research and its procedures; (2) *reasoning* in the process of deciding about participation, with a focus on abilities to compare alternatives in the light of their consequences; (3) *appreciation* of the effects of research participation (or failure to participate) on their own situation; and (4) *expressing a choice* about participation.(3) Whilst an assessment of these abilities is essential, supplemental information may be needed about a candidate's diagnoses, mental status and medical and social circumstances.(3)

The MacCAT-CR provides a format for disclosing selected information on the research project at hand. A standard set of questions then assesses candidates' abilities to understand the information, reason about it, appreciate its consequences and express a choice. The interview samples their abilities using representative content, rather than testing them on the full content of a typical informed-consent disclosure. The MacCAT-CR is based on the structure of the MacArthur Competence Assessment Tool for Treatment.(35) In the MacCAT-CR, the number and focus of questions in each section have been altered to suit a research context. Unlike the MacCAT-T, the MacCAT-CR questionnaire does not have to be individualized for each candidate. This facilitates both the research and the routine use of the interview.

The MacCAT-CR involves two steps: the interview itself (approximately 15, maximal 20 minutes) and the rating. The rating criteria provide a way for the assessing clinician to note opinions on the adequacy or inadequacy of each item response. The MacCAT-CR provides a summary rating for each of the four capacities assessed: 0 to 6 for understanding, 0 to 4 for appreciation, 0 to 8 for reasoning and 0 to 2 for expressing a choice.(3) A serious deficit in any of these abilities may translate to a clinical opinion of incompetence. The scale does not provide 'cut-off scores' that represent competence or incompetence, nor is there an overall MacCAT-CR total score.(3) The ratings provide the assessing clinician with a structured overview of the capacities needed for competent decision making.

In 2008, a Dutch translation of the MacCAT-T was made available by van Eyk.(111) Comments on the use of the MacCAT-T in the Dutch clinical setting were positive: it was judged as practicable and a valuable addition to current competence assessment practice.(112) Before administration, information on the content of the treatment needs to be thoroughly considered by the treating physician, which was viewed as a major advantage. The MacCAT-T aided the physician to structure the information required for the decision making of the individual patient.(112)

In children, research on the MacCAT scales has been limited to two small studies. Koelch used an adapted MacCAT-CR to study the decision-making process in 19 children aged 7 to 15 with psychiatric diagnoses;(28) Tan used the MacCAT-T to study thinking processes in 10 adolescents aged 13 to 21 with anorexia nervosa.(113) Both studies confirmed the feasibility of using the MacCAT scales for children, but neither tested their validity and reliability. More rigorous research is needed on the applicability of the MacCAT instruments for children.

Child-specific factors in competence judgment:

1. Developmental aspects of competence
   In children, decision-making abilities develop over time, as their cognitive, social and emotional abilities advance. Elementary school children develop the capacity for logical, systematic thinking using multiple pieces of information and the ability to perceive underlying reality despite superficial appearance. Cognitive advances, social relationships and emotional development work together to promote moral development in middle childhood and children become increasingly able to consider other people's feelings.(114) But still, they face cognitive limitations: they lack the broad base of knowledge that adults possess. They still sometimes have trouble combining their cognitive skills into a larger problem-solving system. They cannot reason maturely about abstract and hypothetical problems.(115) In adolescence, the brain undergoes substantial change with an increase in efficiency of brain functioning. New cognitive skills such as hypothetico-deductive reasoning – the ability to think of hypothetical solutions and to formulate a systematic plan for deducing which of these solutions is correct – are acquired.(114) Social cognitive changes lead to increased maturity in reasoning about moral issues,(115) giving space to altruism. Even with these advances, compared to adults certain cognitive limitations remain, mostly involving inconsistent application of recently acquired cognitive abilities.(115)
   The ability to balance risks and benefits depends on life experience as well as cognitive abilities. Children's personal experiences of illness and their responses to it can provide them with greater insight and understanding than children of comparable age who lack this experience.(22) Over time, therapeutic relationships with children evolve and children grow and develop, and their response to the experience of illness alters. Competence assessment should respond to those changing circumstances.
2. Provision of information
   Competence can be enhanced by improvement of information provision. Children and adolescents do not have the same comprehension level as adults. Their abilities to read and write and their working memory have not reached optimal growth yet. This implies that the information supply to children should be tailored to their developmental stage. Techniques for communication include both verbal and non-verbal forms of information supply, and breaking up the information into smaller pieces.(22) Information for children needs to be clearly worded,

using simple language, and must connect to the perception of the child. Innovative techniques can contribute to conveying information.(22) Children sometimes need more time.(22)

It has been found in current practice that communication with parents and children is often flawed(116-118) and even that children are incompletely informed.(108) As knowledge is a basic requirement for valid consent,(119) assessment of competence needs to attend to the information process. Competence assessment taking the real-life situation as a starting point, containing the necessary information appropriate to the child's level of development, provides the best basis.

3. Systemic influences

   Growing-up children are, to a greater extent than adults, dependent on other people that surround them, especially their caretakers or parents. An exploration of the systemic influences is indispensable. Children may be particularly susceptible to the influence of parents and health-care professionals due to their need for approval or fear of negative consequences from authority figures.(12;24) Tates states that the communication pattern in medical meetings is dominated by adults, and that physicians' communication is parent-related.(120;121) This illustrates the dependence of children on their parents and physicians for the information supply and level of involvement. Peer relations play an important role in development in middle childhood and adolescence. In interaction with friends, school-age children adhere very closely to peer group norms. In early adolescence, peer influence increases, and then declines.(115) Assessment of competence needs to pay attention to the influences of important others on the child's decision-making process.

Modifications in MacCAT-CR for Children and Adolescents

The original MacCAT-CR by Appelbaum and Grisso(3) was translated into Dutch by a certified professional translator. In the next step the language was adapted to a simple level to be understood by children of elementary school age. We followed the guidelines of BureauTaal to adjust the text to groups with low language skills.(122) An expert on Dutch language and communication, who is also a teacher at the University of Primary Teachers, reviewed the text. Three child psychiatrists and three pediatricians carried out a final review of the text. In our study, the delivery of the interview has been customized to reflect the details of the particular trial in which candidates are asked to participate.

Ditters says in his research that in Dutch clinical practice some wordings of the MacCAT-T interview and scoring manual are not familiar.(112) Some of his interviewers showed difficulties understanding the conceptual framework, and they were uncertain as to when to probe for the right answer. We tackled this problem by applying simple language for the interviewers' instructions and scoring manual as well. We added directions on when and how to probe, providing sample sentences. We aim to make the instrument available to different disciplines. Similarly, the patient information form and the informed-consent form for subjects in this study have been adapted to simple understandable language.

Additional to the worded information, Apppelbaum recommends that subjects be given a card containing the disclosed information for each section and asked to read along as the disclosure is read to them.(3) In children, reading performance, if present, might not have reached adult level. Equally, children might have problems dividing their attention between a written text and a spoken text. We thought it appropriate not to use text cards, and to provide cards with pictures disclosing information about medical procedures unfamiliar to the patient (e.g. an electroencephalogram) instead of written information.

The Dutch version of the modified MacCAT-CR for Children and Adolescents was translated back into English by another certified professional translator. One of the original authors of the MacCAT-CR, Appelbaum, provided comments on this version, which were processed. A special remark needs to be made on a modification to questioning the child's understanding of the consequences of participating in the trial or not. We added the questions: "What do you think your parents will think about it if you take part or don't take part? And what do you think your friends will think?" Scoring the answers, we note whether the child can mention consequences for daily life or social relations. With this approach we give more attention to the influence of social relationships than in the adult version of MacCAT-CR.

Methods/design

This study is a prospective cohort study comparing competence judgment by using observational techniques to outcomes of the MacCAT-CR for Children and Adolescents, while at the same time assessing competency-related patient data.

Methods

The validity and reliability of the translated and modified MacCAT-CR for Children and Adolescents will be assessed in a sample of children who are candidates to participate in ongoing medical trials. A reference standard for competence will be established first. The usual informed-consent procedure will be performed by the clinical investigators, and they will record their own intuitive clinical judgment of a child's consent competence. At this point, parents will also be asked to judge whether their child has understood and is able to make a well-considered decision. This informed consent procedure will be videotaped. The recordings will then be reviewed independently by two experts (child psychiatrists, child psychologists or medical ethicists), who will also record a judgment on the child's consent competence. This will allow us to estimate the inter-examiner reproducibility of the informed-consent procedure.

To establish a reference standard for consent competency, any discordant decisions for a child's consent competency of the two experts and the clinician will be examined. If there is any discrepancy between the three evaluators' judgments, a consensus decision will be reached after discussion. The final decisions will form the reference standard for competence.

After the usual informed-consent procedure, within 48 hours the MacCAT-CR interview will be administered by the researchers, independent of the first clinical judgment; these interviews will also be videotaped. The interviewers consist of specially trained special education or psychology graduates. The interviews will be scored by the administrator and independently by two experts (a multidisciplinary team of child psychiatrists, psychologists and medical ethicists). A yes/no decision will be made following the guidelines in the MacCAT-CR manual.

Demographic patient data will be collected and the Wechsler Nonverbal Scale of Abilities short version will be administered within two months of the interviews.

Objectives

The final objectives are (1) to assess the reproducibility of MacCAT-CR scores and yes/no judgments of competence to consent, and (2) to establish a reference standard to which MacCAT-CR scores can be compared to evaluate the criterion-related validity of the instrument (in the absence of a criterion test for competence to consent). The reference standard will also be used to (1) estimate optimal cut-off scores on the MacCAT-CR scale that

minimizes false positive and false negative decisions, and (2) determine ages for informed consent and compare these to current statutory age limits. The agreement between the reference standard and the judgment of the parent(s) will also be examined.

Subjects

One hundred and sixty pediatric patients aged 6 to 18 who are involved in the selection stages of ongoing medical trials will be recruited. These will be trials that involve heterogeneous groups of children in terms of age and diagnosis (including childhood oncology, lung disease and ophthalmology). The children will be selected consecutively in the order of recruitment for the trials. The lower age limit of 6 is justifiable as younger children cannot be expected in developmental terms to be capable of meaningfully answering the interview questions. Age distribution will be structured in a way that approximately 70% of the sample (± 1 z-score) will be aged 8 to 14, because the transition point in competence is expected to occur there. The purpose is to avoid overestimating reproducibility and criterion validity as a result of excessive contrast in the age distribution. Grounds for exclusion will be insufficient fluency in Dutch.

Measures

The outcome measures of the MacCAT-CR will be a total score, domain scores, and a binary assessment (yes/no) of a child's competence to consent. Clinical investigators and parents will also be asked to give their prior intuitive yes/no assessments of the child's competence to decide.

The Wechsler Nonverbal Scale of Ability short version (WVN) will be used to assess children's intelligence quotient. The WNV is a clinical instrument for examining cognitive capacities of children and adolescents aged 4 to 21. The WVN is suitable for the general population as well as for children with cultural, linguistic, educational or socio-economic varying backgrounds. The subtests do not invoke verbal capacities as instructions are made by pictograms. Different subtests are to be administered in children from 4 to 7 and from 8 to 21. The short version for the first age group consists of matrix reasoning and recognizing, and for the second age group matrix reasoning and spatial orientation.(123) For practical reasons the short version is chosen: the two subtests take 20 minutes together. The full version gives more rigorous outcomes and has psychometrical advantages, but the validity and reliability of the short version are good. In this study the subjects cannot

be burdened by the long version due to possible pain or distress. The WNV is the only IQ test with a standardized short version; this is in contrast to the Wechsler Intelligence Scale for Children. The WNV is approved by the Dutch Committee on Tests and Testing Affairs (COTAN). The WNV will be administered by trained certified professionals (special education or psychology graduates) under supervision of a senior professional.

The highest level of education of the highest-educated parent will be noted as an indicator of socio-economic status. Duration of disease, number of trials previously participated in and ethnicity will be noted.

Informed-consent procedure

Prior written consent to take part in this study will be requested from all child participants and their parents, separate from any consent required of them for the drug trials. The pediatric patients sampled for the drug trials will be informed together with their parents by the trained clinical investigator about the competence study at the same time as they are informed about the drug trial. They will also be free to choose participation in one of the two studies with no consequences for the other. The outcome of the MacCAT-CR interview will not affect the conduct of the drug trial being carried out by the investigator. The ethics committee of the Academic Medical Center Amsterdam in the Netherlands confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and the committee makes no objections to the implementation.

Statistical analysis

Descriptive summaries of demographic and assessment outcome measures will be generated with respect to all subject characteristics.

Reliability: Statistical analysis will include exploration of internal consistency, by estimating Cronbach's alpha for the items of each subscale and for the total scale. We will also calculate adjusted item-to-scale total correlations. Factor analysis and item response theory methods (Rasch analysis) will be used to further test scale unidimensionality. To optimize the MacCAT-CR scoring system and to determine necessary item weights, we will use a specific extension of the Rasch measurement model One Parameter Logistic Model (OPLM).(124) Conditional maximum likelihood estimation methods will be used to obtain stable item parameters.

Criterion-related validity: The overall accuracy of the MacCAT-CR score in classifying competence against the reference standard will be quantified using receiver operator characteristic curve (ROC) analysis. The area under the ROC curve (AUC) will serve as the validity coefficient; this may range from 50% (chance determination) to 100% (perfect determination). The optimal MacCAT cut-off score and the accompanying sensitivity and specificity rates will be determined using Youden's method, the cut-off score corresponding to the fewest false positive and false negative classifications. Against our current expectations, this may give an indication of a single score above which competence is more likely. The validity of the current statutory cut-off ages will be tested by the same method, but using age as the predictor of capacity to provide informed consent.

Inter-rater reproducibility: We will determine inter-rater reproducibility (1) for the clinical judgment on competence to consent by the investigator and the experts, (2) for the MacCAT-CR total and subscale scores, (3) for the yes/no outcome of the reference standard and the yes/no outcome of the MacCAT-CR, and (4) for the yes/no outcome of the reference standard and the yes/no decision of the parents. We will quantify reproducibility with intraclass correlation coefficients for total scores on the MacCAT-CR scales. Inter-rater reproducibility of the item scores will be quantified by calculating weighted Kappa coefficients. To quantify the reproducibility of the yes/no outcome for competence to consent, multi-rater (unweighted) Kappa or simple Cohen's Kappa will be used in the case of pairwise comparisons. We have a special interest in children between 8 and 14 years, and we will compare the ICCs and Kappa values calculated for children in this age group separately.

Statistical power analysis: There is no general agreement about estimating suitable sample size for the psychometric (factor-analytic, Rasch analytic) evaluation of multi-item scales. Simulation studies for the related techniques of regression analysis indicate that a minimum of 10 to 15 observations per variable (item) are needed to obtain stable estimates. For the 13 items of the MacCAT-CR this would result in 130 to 190 observations. Judging from previous studies on MacCAT-CR and MacCAT-T in adults with compromised decisional capacities,(80-83) our proposed sample size of N = 160 is justifiable. In view of the three raters involved in our assessment of inter-rater reproducibility, the intraclass correlation for the MacCAT-CR score can be estimated with ±5% accuracy around the expected level of 0.80 with 95% certainty. The Kappa for the yes/no capacity to consent decision can be estimated with ±11% accuracy and 95% certainty assuming 60% raw agreement between two raters and an expected Kappa of 0.70.

An ROC-AUC validity statistic of 0.80 (null hypothesis AUC 0.69) can be detected with 80% power assuming a 3:1 ratio of test positive (competent to consent) and test negative children. Sensitivity and specificity rates of the MacCAT-CR cut-offs obtained by Youden's method can be estimated with ±7% accuracy, assuming 0.75 as the expected value. For the Rasch analysis, the MacCAT-CR outcomes from the raters will be combined. Data dependency will not be an issue in our use of conditional maximum likelihood estimation methods, because the method makes no assumptions about the distribution of data in the population or about ways in which the sample was selected.

Discussion

Limitations

Due to the lack of a gold standard for competence assessment, the reference standard will be established according to current best clinical practice by physicians that deal with competence assessment in pediatric practice. The expert opinion represents the clinical conception of competence in children. These judgments constitute the best possible starting point. It is possible, however, that competence judgments vary between evaluators. Previous research demonstrates that unaided competence judgments, even of clinicians, are not reliable. Kim describes considerable variety in competence judgments between experienced psychiatrists in a population of geriatric patients asked to participate in a hypothetical trial.(86) Inter-rater reliability with group Kappa statistics ranges from fair to moderate agreement (0.40 to 0.45) for the psychiatrists' judgments. The authors recommend more effective training in the judgment of competence to consent to research, as well as a judgment method. In this study this recommendation has been adopted: the expert panel that is to review the videos will be instructed and provided with basic information on competence judgment.

Another limitation might be that the same version of the MacCAT-CR will be administered to the whole range of children aged 6 to 18. Undoubtedly cognitive abilities and language skills vary widely in this age group. A pilot study did reveal some minor problems in 6-year-old children who did not understand the disclosed information and needed frequent rehearsal. Some of the older children understood easily, and they were not bothered by the simple language level.

Recommendations

A validity study on an assessment tool of competence to consent is badly needed in research practice, particularly in the child and adolescent population. As far as we know, this is the first large-scale empirical study worldwide trying to establish a reference standard for children's competence to consent, combined with validation of an assessment instrument. Results could lead to further development of guidelines, health-care policies and legal policies.

5 Accuracy of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) for measuring children's competence to consent to clinical research

Published as: Hein IM, Troost PW, Lindeboom R, Benninga MA, Zwaan CM, Goudoever JB van, Lindauer RJL. Accuracy of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) for Measuring Children's Competence to Consent to Clinical Research. JAMA Pediatr. 2014 Oct 13;168(12):1147-53. doi:10.1001/jamapediatrics.2014.1694

Abstract

Importance

An objective assessment of children's competence to consent to research participation is currently not possible. Age limits for asking children's consent vary considerably between countries, and, to our knowledge, the correlation between competence and children's age has never been systematically investigated.

Objectives

To test a standardized competence assessment instrument for children by modifying the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), to investigate its reliability and validity, and to examine the correlation of its assessment with age and estimate cutoff ages.

Design, Setting, and Participants

This prospective study included children and adolescents aged 6 to 18 years in the inpatient and outpatient departments of allergology, gastroenterology, oncology, ophthalmology, and pulmonology from January 1, 2012,

through January 1, 2014. Participants were eligible for clinical research studies, including observational studies and randomized clinical trials.

Exposures

Competence judgments by experts aware of the 4 relevant criteria—understanding, appreciation, reasoning, and choice—were used to establish the reference standard. The index test was the MacCAT-CR, which used a semistructured interview format.

Main Outcomes and Measures

Interrater reliability, validity, and dimensionality of the MacCAT-CR and estimated cutoff ages for competence.

Results

Of 209 eligible patients, we included 161 (mean age, 10.6 years; 47.2% male). Good reproducibility of MacCAT-CR total and subscale scores was observed (intraclass correlation coefficient range, 0.68-0.92). We confirmed unidimensionality of the MacCAT-CR. By the reference standard, we judged 54 children (33.5%) to be incompetent; by the MacCAT-CR, 61 children (37.9%). Criterion-related validity of MacCAT-CR scores was supported by high overall accuracy in correctly classifying children as competent against the reference standard (area under the receiver operating characteristics curve, 0.78). Age was a good predictor of competence on the MacCAT-CR (area under the receiver operating characteristics curve, 0.90). In children younger than 9.6 years, competence was unlikely (sensitivity, 90%); in those older than 11.2 years, competence was probable (specificity, 90%). The optimal cutoff age was 10.4 years (sensitivity, 81%; specificity, 84%).

Conclusions and Relevance

The MacCAT-CR demonstrated strong psychometric properties. In children aged 9.6 to 11.2 years, consent may be justified when competence can be demonstrated in individual cases by the MacCAT-CR. The results contribute to a scientific underpinning of regulations for clinical research directed toward children.

This prospective study of consent in children determines that competence can be demonstrated in individual cases by the MacArthur Competence Assessment Tool for Clinical Research in those aged 9.6 to 11.2 years.

Introduction

At present, more than 50% of drugs prescribed to children have not been tested in their age group.(125) Prescribers often have no alternative but to extrapolate to children the doses of drugs registered for adults. Historically the protection of children from research was often translated as simply excluding them from trials.(7) Research with this vulnerable population involves many unique ethical and legal considerations. Little is known about children's capacities to meaningfully decide on research participation. To our knowledge, the correlation between competence and age in children has never been systematically investigated.

Strictly speaking, competence to consent denotes a legal status, representing an informed, free, self-determined choice based on understanding and rational reasons.(1) Competence is task and context specific.(1) Incompetence should, in principle, be determined by a court; however, good pragmatic reasons exist to continue the traditional practice of having clinicians determine patients' competence.(2) In clinical practice, competence is generally addressed as decision-making capacity.(3) In this article we use the terms interchangeably; unless otherwise specified, we are referring to clinical assessment of capacity.(3)

The reliability of unstructured competence assessments has been poor because clinicians may not know which standard to apply. Age standards prescribed by law may have too much influence. Clinicians tend to judge a child as competent if the child's decision conforms to their own ideas of the child's best interest.(107;108) Providing clinicians with the generally accepted legal standards for competence improves their judgments and increases interrater agreement.(2) These legal standards embody the following 4 capacities: to communicate a choice, to understand the relevant information, to appreciate the medical consequences of the situation, and to reason about treatment choices. Clinicians aware of the relevant criteria should be able to assess a patient's competence.(26)

The first objective of our study was to develop a standardized competence assessment instrument for children in clinical research, including drug trials. The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)(3) has been evaluated as the best competence assessment

instrument for adults. We modified the instrument to be more applicable for children. First, we assessed the reproducibility and validity of the child version of the MacCAT-CR. Second, we examined the dimensionality of the instrument. The MacCAT-CR is clearly not designed to provide an overall total score or a cutoff score because the instrument is structured according to the 4-capacities model of decision making. However, we hypothesized that when the scores on the 4 domains unexpectedly constitute a single trait or continuum of competence, estimation of cutoff scores above which competence is likely should be possible. This hypothesis may further objectify decisions regarding a child's competence based on the modified instrument.

The international statutory age limits for deeming a child legally competent to give informed consent in clinical research vary widely, just as they vary within the United States and Europe.(102) Legal interpretations at a local level may present an age limit below which children are considered by definition to be incompetent to act for themselves and may express their agreement as assent.(126) Lower age limits vary from 7 to 18 years.(102;126) Some jurisdictions present 2 age limits, and for children and adolescents between these limits, consent is required from the children and parents, provided the children are competent to decide. An upper age limit presenting an age above which adolescents are deemed adult in medical decision making varies from 15 to 18 years.(102;126) To deal with discrepancies between jurisdictions, we studied the capacities of children and adolescents (hereinafter referred to as children) for consent regardless of their age and legal status. A final objective was to provide empirical evidence regarding the age cutoffs for presuming competence to consent in children.

Methods

Patient Population

From January 1, 2012, through January 1, 2014, we enrolled a cohort of 161 pediatric inpatients and outpatients eligible for clinical research from hospitals in Amsterdam, Rotterdam, and the Hague, the Netherlands (participating institutions are listed in Table1). The inclusion criterion was age 6 to 18 years. We included children who decided to participate in the clinical research and children who refused. The only exclusion criterion was not speaking Dutch. The research design and methods have been described comprehensively elsewhere by Hein and colleagues.(4)

The study procedures were judged by the institutional review boards of the participating institutions, and all approved. Prior written consent was obtained from participants 12 years or older and all parents.

Competence Assessment

As the index test for competence assessment, we used the semistructured interview format MacCAT-CR developed by Appelbaum and Grisso in 2001.(3) The MacCAT-CR measures the following 4 aspects of decision-making capacities that reflect the standards for competence in most jurisdictions: (1) understanding the disclosed information about the nature and procedures of the research; (2) reasoning in the process of deciding about participation, with a focus on abilities to compare alternatives in the light of their consequences; (3) appreciation of the effects of research participation on the patient's own situation; and (4) expressing a choice about participation.[5] The MacCAT-CR combines information disclosure with competence assessment in approximately 15 minutes. It provides subscale scores but does not offer a total score or a cutoff. The ratings provide the clinician with a structured overview.

Of a variety of operational translations of the concept of competence into assessment instruments, the MacCAT-CR receives the most empirical support.(32) Studies in populations with dementia, mental disabilities, and psychiatric disorders show initial indications of validity(35) and a high degree of reliability.(80) The Dutch version of MacCAT-CR was modified for children with the approval of Paul S. Appelbaum, MD.(4) Modification included the use of simple language to be understood by elementary school–aged children and added questions on the influence of social relationships (ie, in the reasoning domain, "How do you think your parents will feel about you participating or not participating? And how do you think your friends will feel about it?" has been added)(4) (proprietary issues preclude publication of the version used). Face validity and feasibility were confirmed in a pilot study including 10 children aged 6 to 18 years (I.M.H., P.W.T., R.L., and R.J.L.L.; unpublished data, December 2011). We used competence judgments by clinicians aware of the relevant criteria to establish the reference standard, as is generally accepted best practice.(26)

Procedure

Children and parents were informed about the clinical research in the conversation with the clinical researcher (including M.A.B. and C.M.Z.), who asked for informed consent. This conversation was videotaped and

served as the basis for establishing the reference standard (see below). Within 2 weeks, an interviewer from a panel of experts (listed at the end of the article) administered a MacCAT-CR interview to the child. This interview was also videotaped and rated afterwards.

The panel of 14 experts (including I.M.H., P.W.T., M.A.B., C.M.Z., and R.J.L.L.) consisted of trained pediatricians, child psychiatrists, child psychologists, research nurses, a medical ethicist, and a jurist. The 3-hour training included instructions on competence judgment by the 4 relevant criteria and joint practicing through 3 videos of the conventional informed consent conversation together with instruction on rating the MacCAT-CR and joint rating of 2 videos of MacCAT-CR interviews. In addition, the expert panel practiced by judging 3 videos that were removed from the analysis to exclude bias through a learning effect.

Each member of the panel independently rated a number of conventional informed consent conversation videos and a number of MacCAT-CR interview videos that were presented in random order and reciprocally blinded. For establishing the reference standard, each video from the conventional informed consent conversation was rated by 2 different experts. Each MacCAT-CR interview video was rated by 3 different experts to assess the reproducibility. For all videos, the experts gave their judgment consisting of 1 of the following 4 categories: very likely competent, probably competent, probably incompetent, and very likely incompetent. We considered competence to be present when an expert gave a judgment of very likely or probably competent.

Sample Size Requirements

No general agreement exists about estimating a suitable sample size for the psychometric evaluation of multiple-item scales. Simulation studies for the related techniques of regression analysis indicate that a minimum of 10 to 15 observations per variable (item) are needed to obtain stable estimates.(127) The 13 items of the MacCAT-CR therefore would require 130 to 190 observations. Judging from previous studies on MacCAT scales in adults with compromised decisional capacities,(4;81-83) our proposed sample size of 160 is justifiable.(4)

Statistical Analysis

Reproducibility of MacCAT-CR Item and Domain Scores

Reproducibility of the MacCAT-CR item scores for the sets of 3 raters was evaluated using weighted κ coefficients. Because 3 different raters scored the MacCAT-CR and because calculation of a weighed κ statistic for more

than 2 raters is not possible, the multirater-weighted κ value for each item was calculated using intraclass correlations.[19] Reproducibility of the MacCAT-CR domain scores was also evaluated using intraclass correlations (model 1, single measures).

Dimensionality of the MacCAT-CR

We examined dimensionality by using internal consistency analysis on the mean scores of the 3 raters. We examined the item-rest correlations, also known as *corrected item-total correlation*, which refers to the correlation between the item score and the total sum of the remaining items, excluding the item. Item-rest correlations less than 0.30 indicate that the item does not sufficiently contribute to the reliability of the scale and may be discarded. If a positive relation could be demonstrated for all items on the subscale and total scale levels, factor analysis (principal components) with eigenvalues greater than 1 criterion and visual inspection of the scree plot were used to further examine dimensionality of the MacCAT-CR. Subsequently, we used item response theory methods, a specific extension of the Rasch measurement model,(124) to confirm scale unidimensionality. Conditional maximum likelihood estimation methods were used to estimate the item and person (MacCAT-CR competence ability level) variables. Fit of the data to the unidimensional extended Rasch model was tested using item-oriented fit statistics (S tests)[20] that examine observed and expected numbers with a given item score conditional on competence ability level as measured with the MacCAT-CR. Overall fit of all item scores to the unidimensional model was tested with the R1c statistic.(124) For all fit statistics, $P > .05$ indicates fit to the unidimensional measurement model.

Rasch analysis was performed on the pooled MacCAT-CR scores using all interrater MacCAT-CR scores and on the scores of children who responded to all the MacCAT-CR items (excluding children with missing scores on ≥1 item) because the method requires a large number of observations, preferably more than 300. Because we used conditional maximum likelihood estimation methods, dependence between scores is not an issue; the method makes no assumptions on how the sample was selected or on the distribution of abilities in the sample.(128)

Accuracy of the MacCAT-CR and Estimation of the Cutoff for Competence

The overall accuracy of the MacCAT-CR total score (in case of unidimensionality) in classifying competence against the reference standard was quantified using receiver operator characteristics curve analysis. The area under the receiver operating characteristic curve (AUC) served as the validity coefficient;

AUCs exceeding 0.70 are generally considered adequate. The optimal MacCAT-CR cutoff score and the accompanying sensitivity and specificity rates were determined using the Youden method, representing the score corresponding to the fewest false-positive and false-negative classifications.(129) For a few trials in which some MacCAT-CR items were not applicable (ie, when no placebo was used in the trial), we computed adjusted scores, calculated as the obtained score divided by the fraction of items completed, for the analysis.

Estimation of Cutoff Ages

The validity of the current statutory cutoff ages was tested by the same method. In this estimation, we used age as the predictor of competence to consent.

Results

Baseline Characteristics

Of the 209 children eligible for this study, 48 were excluded or were unavailable to participate for various reasons (Figure 3). Baseline characteristics of the 161 participants who entered analysis are listed in Table 1. Mean age was 11 (median, 10.0 [range, 6-17]; SD, 2.8; 25th to 75th percentiles, 9-12) years. Of the 6 children unable to complete the whole interview, 4 were 6 and 2 were 7 years of age. In the age range of 8 to 18 years, feasibility was very high. The interval between the reference test and MacCAT-CR exceeded 2 (maximum, 6) weeks on 9 occasions.

Figure 3.

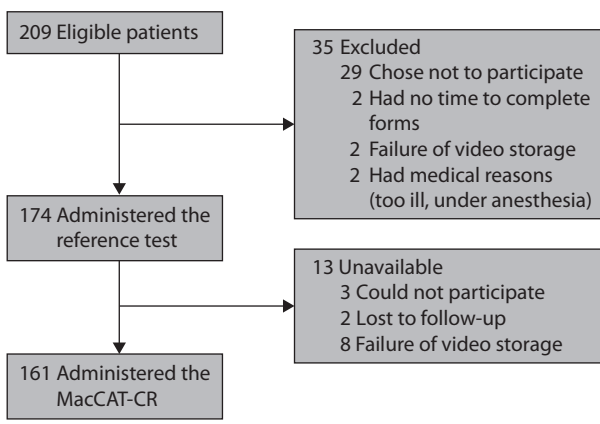


Table 1. Baseline Characteristics of Study Participants

Characteristic	Participant Data (n = 161)[a]	Age, Mean (Range), y
Male sex	76 (47.2)	11 (6-17)
Research project		
Department of Allergology, 1 RCT	3 (1.9)	8 (6-11)
Department of Gastroenterology, 1 RCT and 3 observational studies	29 (18.0)	14 (10-17)
Department of Oncology, 4 RCTs	10 (6.2)	10 (6-16)
Department of Ophthalmology, 2 RCTs	113 (70.2)	10 (6-17)
Department of Pulmonology, 2 RCTs	6 (3.7)	8 (6-10)
Hospital[b]		
Academic Medical Center, Amsterdam	31 (19.3)	
Erasmus Medical Center, Rotterdam	6 (3.7)	
Havenziekenhuis, Rotterdam	6 (3.7)	
VU University Medical Center, Amsterdam	5 (3.1)	
Westeinde Hospital, the Hague	113 (70.2)	
Trial participation[c]		
Yes	64 (40.0)	11 (6-17)
No	62 (38.8)	10 (6-17)
Unknown	34 (21.3)	10 (6-17)
Duration of illness, mean (SD), mo	30.51 (39.05)	
Trial experience[c]		
Yes	38 (23.8)	11 (6-17)
No	122 (73.3)	11 (6-17)
Educational level of participant[d]		
Elementary	117 (72.7)	NA
Middle	41 (25.5)	NA
High	3 (1.9)	NA
Highest educational level of parent(s)[c,d]		
Elementary	17 (10.6)	NA
Middle	76 (47.5)	NA
High	67 (41.9)	NA
Ethnicity		
Western Europe	91 (56.5)	NA
Middle East	48 (29.8)	NA
Surinam/Antillean	20 (12.4)	NA
Other	2 (1.2)	NA

Abbreviations: NA, not applicable; RCT, randomized clinical trial.

[a]Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b]All hospitals were located in the Netherlands.

[c]Data were missing for 1 participant.

[d]Elementary includes no primary school, primary school, special primary school, and special secondary school. Middle includes preparatory secondary vocational education, secondary vocational education, senior general secondary school, and preparatory scientific education. High includes college and university.

Reproducibility of MacCAT-CR Item and Domain Scores

Reproducibility of the MacCAT-CR item scores for the sets of 3 raters, expressed in weighted κ values, are listed in Table 2. The intraclass correlation coefficient for the MacCAT-CR total score was 0.91; for the Understanding subscale, 0.92; for the Appreciation subscale, 0.84; for the Reasoning subscale, 0.68; and for the Choice subscale, 0.80. Weighted κ values for individual items ranged from 0.52 (item 11) to 0.82 (item 7).

Table 2. Reproducibility and Internal Consistency of MacCAT-CR Item and Domain Scores

Domain, Item No.	Weighted κ Value (95% CI)	Subscale ICC Coefficient (95% CI) [α Value]	Item-Rest Correlation[a]	
			Domain Score	Total Score
Understanding				
1	0.61 (0.53-0.69)	0.92 (0.90-0.94) [0.82]	0.70	0.66
2	0.78 (0.72-0.83)		0.65	0.61
3	0.63 (0.55-0.70)		0.75	0.75
4	0.74 (0.67-0.79)		0.74	0.84
5	0.80 (0.75-0.85)		0.66	0.71
Appreciation				
6	0.57 (0.48-0.66)	0.84 (0.79-0.87) [0.73]	0.59	0.61
7	0.82 (0.77-0.86)		0.54	0.64
8	0.81 (0.75-0.85)		0.53	0.75
Reasoning				
9	0.72 (0.65-0.78)	0.68 (0.61-0.74) [0.80]	0.80	0.77
10	0.69 (0.62-0.75)		0.68	0.63
11	0.52 (0.43-0.61)		0.48	0.55
12	0.72 (0.65-0.77)		0.51	0.65
Choice[b]				
13	0.80 (0.75-0.84)	NA	NA	0.47

Abbreviations: ICC, intraclass correlation coefficient; MacCAT-CR, MacArthur Competence Assessment Tool for Clinical Research; NA, not available.

[a]Indicates the correlation between the item score and the total sum of the remaining items, excluding the item. Item-rest correlations of less than 0.30 indicate that the item does not sufficiently contribute to the reliability of the scale and may be discarded.

[b]No subscale ICC or α value could be calculated because this domain has only 1 item.

Dimensionality of the MacCAT-CR

The Cronbach α for the total MacCAT-CR scale considering all 13 items was 0.89. Item-rest total score correlations ranged from 0.47 to 0.84 (median,

0.65) (Table 2). The Cronbach α values for the subscales (Understanding, 0.82; Appreciation, 0.73; and Reasoning, 0.80) indicated good internal consistency.

Factor analysis showed that 1 component had an eigenvalue greater than 1, namely 6.8, explaining 53% of the total score variation. Factor loadings ranged from 0.54 to 0.89. The remaining 12 factors each explained 1% to 7% of the total variation. Subsequent Rasch analysis on the 21 individual MacCAT-CR question scores (n = 384) confirmed unidimensionality (R1c goodness of fit χ^{260}, 60.7; P = .45).

Overall Accuracy of Unidimensional MacCAT-CR

By the reference standard, 54 children (33.5%) were judged incompetent; by the MacCAT-CR, 61 children (37.9%). Because unidimensionality of the MacCAT-CR was supported, we determined the overall accuracy of the MacCAT-CR total score in classifying competence against the reference standard as 0.78. The optimal cutoff for the MacCAT-CR total score above which competence is likely was 35 points. Accompanying sensitivity was 63%; specificity, 85%; positive predictive value, 79%; and negative predictive value, 72%.

Age Cutoffs

Age was a good predictor of competence on the reference standard (AUC, 0.84) and on the MacCAT-CR (AUC, 0.90). The cutoff age with 90% sensitivity was 9.0 years for the reference standard and 9.6 years for the MacCAT-CR. The cutoff age with 90% specificity was 11.5 years for the reference standard and 11.2 years for the MacCAT-CR. The optimal cutoff age with the fewest false-positive and false-negative classifications on the MacCAT-CR was 10.4 years (sensitivity, 81%; specificity, 84%).

Discussion

We have confirmed the accuracy of the MacCAT-CR for assessing children's competence to consent. Results of this study in children aged 6 to 18 years provide evidence of reliability (reproducibility) and validity.

In children, our results suggest that MacCAT-CR scores on the 4 domains constitute a single trait or continuum of competence. This finding allows for estimating a cutoff score on the MacCAT-CR above which competence

in children is likely. The demonstrated unidimensionality of the MacCAT-CR in children does not align with the adult literature stating that scores on subscales need to be weighted independently and that failure on one domain could translate into a judgment of incompetence.(3;80)

Competence assessed by the MacCAT-CR strongly correlates with age, with an overall accuracy of 0.90. The MacCAT-CR demonstrated 90% sensitivity for competence classification before 9.6 years and 90% specificity after 11.2 years. The range from 9.6 to 11.2 years of age constituted a changeover. This finding aligns with those of previous research to suggest that clinical competence to consent to medical interventions can be present in children younger than 12 years.(23;106) However, the age categories resulting from our study do not coincide with age limits in many jurisdictions. Applying a format that uses the 3 age categories developed by Grisso and Vierling(12) to our results would imply that asking for consent from children younger than 9.6 years might not be justified. Assuming that children older than 11.2 years cannot provide competent consent appears to have no ground. Children aged 9.6 to 11.2 years appear to be in a transition period; they develop important capacities but their maturity is not pervasive. In children around these ages, consent may be justified when competence can be demonstrated in individual cases.(12) A tailored informed consent process and competence assessment by the MacCAT-CR can support these children in decision making; at the same time, the process could preempt the pitfall of imposing complex research decisions on children who are not able to make them. Generalizability of the study results is credible because the study population was heterogeneous.

This study has specific limitations. An assessment instrument is not meant to replace clinical judgment but to complement its accuracy. The expert judgment based on the videos might have been biased by the lack of all the required information in the unstructured conversations.

In light of the heterogeneity of the sample, interpretation of the data is subject to insufficiencies. Participants were enrolled in any type of clinical research, with expected differences in the complexity of the studies. This difference could render age limits resulting from our study less applicable to special patient groups. Further reporting on complexity, intelligence, prior trial experience, duration of illness, and other variables is under preparation (I.M.H., P.W.T., R.L., J.B.v.G., R.J.L.L., unpublished data, June 2014).

Duration between the reference and index tests exceeded the 48 hours planned originally for practical reasons. However, because the MacCAT-CR includes information disclosure, recall of information would not have been a problem.

Conclusions

Our modified version of the MacCAT-CR demonstrated accuracy in assessing children's competence to consent; psychometric properties in children aged 6 to 18 years were strong. Results indicate a strong correlation of competence with age. In children younger than 9.6 years, competence is unlikely; in children older than 11.2 years, competence is probable. In children aged 9.6 to 11.2 years, consent may be justified when competence can be demonstrated in individual cases, and we suggest competence assessment by the MacCAT-CR for these children. The results provide objective starting points for policymakers and contribute to a scientific underpinning of parliamentary proposals to modify the regulations for clinical research in children.

Directions for future research include investigating children's competence in different types of medical research situations and correlations of competence with other variables. More research on children's competence in special research populations (ie, child and adolescent psychiatric and mentally disabled populations) is recommended. For treatment settings, we recommend research with the MacArthur Competence Assessment Tool for Treatment modified for children.(134)

6 Key factors in children's competence to consent to clinical research

Hein IM, Troost PW, Lindeboom R, Benninga MA, Zwaan CM, Goudoever JBv, Lindauer RJL
Submitted

Abstract

Objectives

Age is frequently assumed to be the best parameter to assess children's competence to consent, however internationally statutory age limits for asking children's consent to clinical research differ widely and other factors may be more predictive. We examined potential determining factors for children's competence to consent and to what extent they contribute.

Methods

Design
Prospective study from January 1, 2012 through January 1, 2014, on association and predictive value of possible explanatory variables for children's competence to consent.

Setting
In- and outpatient departments of allergology, gastroenterology, oncology, ophthalmology and pulmonology.

Patients
Pediatric patients aged 6 to 18 years eligible for clinical research studies.

Interventions
Children's competence to consent was assessed by MacArthur Competence Assessment Tool for Clinical Research. Variables included intelligence, disease experience, risk and complexity of decision, ethnicity, socio-economic status (SES) and parental competence judgment.

Main outcome measures
Association and predictive value of the variables with competence.

Results

Out of 209 eligible patients, 161 were included (mean age, 10.6 years, 47.2 % male). Age, SES, intelligence, ethnicity, parental competence judgment and trial participation showed an association with competence ($P<0.05$). Only age and intelligence were strongly associated, with Wald statistic 27.7 and 11.2 respectively. Age demonstrated the highest predictive value (area under the receiver operating characteristic curve 0.90).

Conclusions

Age is the most accurate determining factor for children's competence to consent. Experience with disease and prior trial participation did not show to contribute to competence in this study, nor did other variables. This underlines the relevance of the previously found age limit of 11.2 years for children to be generally competent.

Introduction

The informed consent model assigns patients autonomy over medical interventions, including self-determination with regard to research participation. Exercising this autonomy regularly imposes burden of considerable responsibility on patients. Historically the protection of children from research was often translated as simply excluding them from trials.(7) Research with this vulnerable population involves unique ethical and legal considerations. However, little is known about children's capacities to meaningfully decide on research participation. The composition of children's clinical competence to consent is currently not fully understood. Most laws present age limits for children to exercise their patient rights, however in pediatric clinical practice age limits often do not reflect the ability of an individual child.(4) For clinicians it is critical to strike a proper balance in order both to protect children's interests when they are not fully able to do so themselves and to respect their autonomy when they are.

Competence is task- and context specific, meaning that assessment of competence should be regarded as a specific judgment at a specific moment of the ability of the patient to fulfill the concrete task that he is facing.(1) A

competent decision represents an informed, free, self-determined choice, which applies to informed consent as well as to informed refusal. Adult patients are deemed competent unless the clinician has reasons to believe otherwise. Children however, are not accorded this presumption of competence in most jurisdictions. Strictly speaking incompetence denotes a legal status that in principle should be determined by a court, however resorting to judicial review in every case of suspected incompetence would very heavily burden both the medical and legal systems, therefore there is good reason to continue the traditional practice of having clinicians determine patients' competence.(38) In clinical practice competence is generally addressed as decision-making capacity.(3) In this article we use the terms interchangeably, and unless otherwise specified we are referring to clinical assessment of capacity and not legal determination of competence.(3)

Child-specific factors in competence judgments are developmental aspects, systemic influences and adequate information provision.(4) Firstly; developmental aspects comprise cognitive advances, social relationships and emotional development together with moral development acquired in middle childhood, and hypothetico-deductive reasoning acquired in adolescence. Despite these advances, compared to adults certain cognitive limitations remain, mostly involving inconsistent application of recently acquired cognitive abilities.(115) Children's personal experiences of illness and their responses to it can provide them with greater insight and understanding than children of comparable age who lack this experience.(22) Secondly; growing-up children are, to a greater extent than adults, dependent on other people that surround them, and may particularly be susceptible to the influence of parents and health-care professionals due to their need for approval or fear of negative consequences from authority figures.(24) In early adolescence there is an increase of peer influences, which then declines.(12) Thirdly; children's competence relies greatly on clearly worded information, using simple language, connecting to the perception of the child, containing all the necessary information appropriate to the child's level of development.(22)

Although age is frequently assumed to be the best feasible parameter to assess children's competence to consent, internationally the statutory age limits for asking children's consent to research participation differ widely. Some jurisdictions apply two age limits: the lower age limit varies from seven to fifteen years, the upper age limit is set at seventeen or eighteen years.(102) Children younger than the set age limit are considered by definition incompetent to act for themselves, they can express agreement by giving assent.(126) Previous studies have shown that age is at best a proxy

for developmental capacity(23;131;132) and other key determining factors are highlighted. Cognitive development, experience, and dependence on parents and peer influences are the child-specific factors we described above. Additionally, the impact of the level of complexity and risk of the decision, ethnicity and socioeconomic status (SES) are mentioned in literature(4;24) to be potential determining factors.

In our present study we examine which are key determining factors for children's competence to give informed consent to clinical research and to what extent they contribute.

Patients and Methods

Patient population

The details of the study participants and baseline characteristics are comprehensively described elsewhere.(150) Briefly, between January 1, 2012 and January 1, 2014 a cohort of 161 pediatric inpatients and outpatients between 6 and 18 years of age were enrolled, visiting hospitals in Amsterdam, Rotterdam and The Hague (the Netherlands). Inclusion criteria were eligibility for clinical research participation and speaking Dutch. The clinical research projects at offer were ten randomized controlled trials and three observational studies at departments of allergology, oncology, pulmonology, ophthalmology and gastroenterology. The study protocol was approved by the institutional review boards at each site. Prior written consent was obtained from participants 12 years or older and all parents.

Methods

Children's competence was assessed by the MacCAT-CR interview. The MacCAT-CR guides clinicians and patients through the process of information disclosure required for informed consent, combined with an assessment of the patient's capacities, in approximately fifteen to twenty minutes. The Dutch version of MacCAT-CR was modified for children by using simple language to be understood by children of elementary school age, and adding questions on the influence of social relationships.(4) We demonstrated that children's competence to consent to clinical research can reliably and validly be assessed by the MacCAT-CR.(150)

A MacCAT-CR competent classification was considered present when at least two out of three of the experts rated the MacCAT-CR interview positive for competence, in other cases patients were classified incompetent. Additional patient data were collected, demographic characteristics included ethnicity. Number of trials previously participated in and duration

of disease were measures used to express disease experience. Disease experience was arbitrarily categorized as low (no prior trial participation and duration of disease less than one month), moderate (no prior trial participation and duration of disease more or equal to one month) or high (prior trial experience). The level of education of the highest educated parent served as an indicator of SES, which we categorized: low (no primary school, primary school, special primary school, special secondary school); middle (preparatory secondary education, secondary vocational education, senior general secondary school, preparatory scientific education); high (college, university). Complexity and risk of the decision was categorized into subgroups by consensus between three researchers (LG, IH, PT): low (no risk, no blinding), moderate (little risk, placebo and blinding) or high (possible risk, serious disease, complex or disagreeable research procedure, placebo and blinding). Cognitive capacities were expressed as intelligence quotient (IQ) and assessed by the Wechsler Nonverbal Scale of Ability short version (WNV). The WNV is a clinical instrument for examining cognitive capacities of children and adolescents aged 4 to 21, which is suitable for the general population as well as for children with cultural, linguistic, educational or socio-economic varying backgrounds. The subtests do not invoke verbal capacities as instructions are made by pictograms, and the validity and reliability of the short version are good. The WNV was administered by trained certified professionals (special education or psychology graduates) under supervision of a senior professional. Scores on the WNV could be categorized into three IQ categories: low (under 90), average (90-110) or high (110 or higher). Ethnicity was classified as Western European, Middle East, Surinam/Antillean or other, based on the country of origin of the accompanying parent.

Parent(s) were asked if they judged their child competent to give independent consent. We classified if the child decided to participate in the research project at offer or not, or if he/she had not decided yet.

Data analysis

Multiple logistic regression analysis was used to examine to what extent the explanatory variables age, gender, disease experience, SES, complexity and risk, intelligence, ethnicity, parental competence judgment and decision on trial participation were related with competence. First we examined the distribution of these variables in the sample to detect empty cells in contingency tables and collapsed categories to avoid empty cells or low frequency cells ($n < 5$) when necessary. Ethnicity classifications were collapsed into Western European and other ethnicity. All explanatory variables

were entered simultaneously into the model to examine which variable contributed most to the probability for competence to consent. Since adjusted odds ratio for the variables depend on their scale of measurement, we used the Wald-statistic as a measure of strength of the association with competence.

Calibration of the model was examined using the procedure of Hosmer and Lemeshow(129) that test the differences between expected model probabilities and observed probabilities of competence to consent. A HL-test p-value > .05 indicates no statistically significant differences between observed and expected frequencies with a competent classification and thus acceptable model fit. Accuracy of the model was examined by receiver operating characteristic curve analysis. The area under the ROC curve (AUC) indicates the accuracy of the model; it may range from 50% (chance determination) to 100% (perfect determination). AUCs exceeding .70 are generally considered adequate.

Results

Baseline characteristics

Characteristics of the study participants were described elsewhere,(133) we will give a brief overview: of the 209 eligible children eligible for this study, 161 were enrolled, mean age 10.6 years (range, 6-18).

Association of variables with competence

The distribution of the variables in contingency tables are demonstrated in Table 3. A higher age, higher SES, average IQ, Western ethnicity, a parental judgment of competence and a positive decision to participate in research were variables positively associated with competence to consent ($P<0.05$).

Strength of associations

The independent contribution of each characteristic to the probability of competence to consent is listed in Table 4. Age and IQ showed highest Wald statistics (age 27.7, low IQ 11.2, average IQ 8.5, high IQ 9.2) and were most predictive for competence classifications: higher age and average or high IQ were positively associated to competence.

The Hosmer and Lemeshow goodness of fit P-value was $P=.81$. There were small differences between expected model probabilities and observed probabilities for competence (overall correct > 87%).

Table 3. Distribution of variables among competent and incompetent children

	Total (N=161)	Competent (n= 100)	Incompetent (n= 61)	Odds ratio (95% CI)	P
Mean age in years (SD)	10.6 (2.8)	12.4 (2.4)	8.9 (1.6)	-	<0.001
Male, N (%)	76 (47)	44 (44)	32 (53)	1.4 (0.74-2.66)	-
Disease experience, N (%)					
Low*	49 (30)	31 (31)	18 (30)	1.00	-
Medium	74 (46)	44 (44)	30 (49)	0.85 (0.41-1.80)	0.67
High	38 (24)	25 (25)	13 (21)	1.12 (0.46-2.71)	0.81
SES, N (%)					
Low*	18 (11)	6 (6)	12 (20)	1.00	-
Middle	76 (47)	47 (47)	29 (48)	3.20 (1.10 – 9.6)	0.03
High	67 (42)	47 (47)	20 (33)	4.70 (1.55-14.3)	0.006
Complexity and risk, N (%)					
Low*	29 (18)	28 (28)	1 (2)	1.00	-
Moderate*	113 (70)	62 (62)	51 (84)	1.00	-
High	19 (20)	10 (10)	9 (15)	0.64 (0.25 -1.68)	0.37
IQ, N (%)					
Low*	52 (32)	24 (24)	28 (46)	1.00	-
Average	66 (41)	44 (44)	22 (36)	2.33 (1.11-4.93)	0.03
High	43 (27)	32 (32)	11 (18)	3.39 (1.41 -8.15)	0.06
Ethnicity, N (%)					
Western European*	91 (56)	64 (64)	27 (44)	1.00	-
Other[a]	70 (44)	36 (36)	34(56)	0.45 (0.23-0.86)	0.02
Parental competence judgment					
Incompetent*	34 (21)	7 (7)	27 (45)	1.00	-
Competent	125 (79)	92 (93)	33 (55)	10.8 (4.3-27.0)	<0.001
Decision to participate					
No	62 (39)	34 (34)	28 (47)	1.00	-
Yes	64 (40)	48 (48)	16 (27)	2.5 (1.2-5.3)	0.02
Do not know	34 (21)	18 (18)	16 (27)	0.9 (0.4-2.1)	0.86

*(Combined) reference category, [a] Other: Middle East (30%), Surinam/Antilles (13%) and "other"(1%)

Table 4. Association of variables with competence

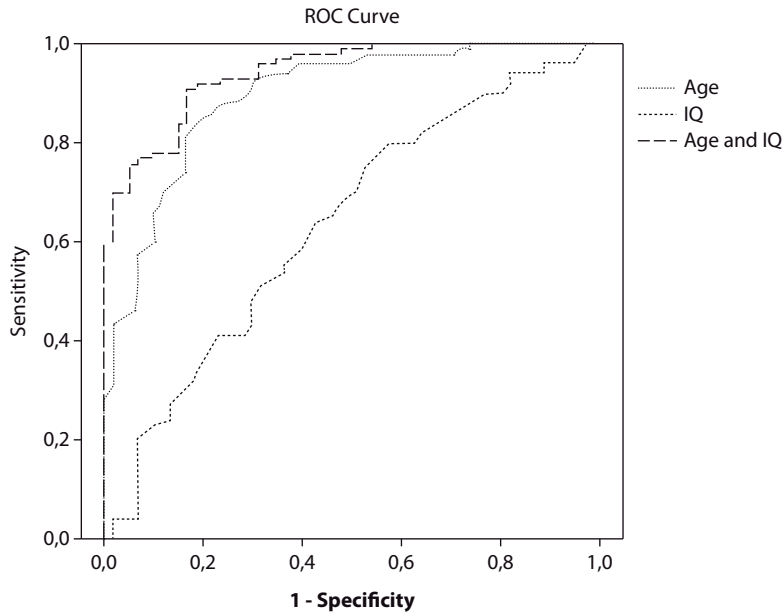
	B (SE)	Wald	Corrected Odds Ratio (95% CI)
Age	1.37 (SE)	27.66	3.9 (2.4-6.5)
Gender	0.37	0.38	1.5 (0.4-4.8)
Disease experience			
Low*	0	1.73	1
Medium	0.62	0.80	1.9 (0.5-7.2)
High	-0.34	0.18	0.7 (1.4-3.5)
SES			
Low*	0	0.98	1
Middle	0.21	0.05	1.2 (0.2-8.0)
High	0.91	0.66	2.5 (0.3-22.2)
Complexity and risk			
Low*	0	0.25	1
Moderate	-0.78	0.12	0.5 (<0.01-36.9)
High	-1.10	0.23	0.3 (<0.01-29.5)
IQ			
Low*	0	11.23	1
Average	2.45	8.54	11.6 (2.2-59.9)
High	2.96	9.24	19.3 (2.9-130.4)
Ethnicity			
Western*	0	-	1
Other	-0.56	0.60	0.57 (0.1-2.3)
Parental competence judgment			
Incompetent*	0	-	1
Competent	1.38	2.72	3.96 (0.8-20.3)
Decision to participate			
No*	0	2.43	1
Yes	1.38	2.41	3.99 (0.7-22.9)
Do not know	0.52	0.49	1.66 (0.4-7.1)

*Reference category

Accuracy of associated variables

We further examined the predictive value of age and IQ using the area under the ROC curve (AUC) as a measure of accuracy: IQ demonstrated an AUC of 0.64 (95% CI 0.54-0.71); age 0.90 (95% CI 0.84-0.94); age and IQ combined showed an AUC 0.93 (0.90-0.97) (Figure 4). The AUC of the total model including al predictive variables was 0.95 (95% CI 0.93-0.98).

Figure 4. Predictive value of age and intelligence on competence



Discussion

Results showed that age is the key determining factor that can predict children's competence to consent with a high accuracy. Higher IQ is not predictive on its own, combined with age it adds a little to the predictive value. Other potential explanatory variables gender, disease experience, SES, complexity and risk of the decision, ethnicity, parental competence judgment and decision to participate did not contribute significantly to children's competence to consent.

The high accuracy of age as a predictor of children's competence to consent complements to recent findings on age limits.(150) Earlier work showed that competence to consent was unlikely in children younger than 9.6 years and in those older than 11.2 years, competence was probable.(150) These findings offer underpinnings for appropriate age limits in policies regarding children's consent.

Cognitive development was described in theoretic literature to play a major role in children's competence.(132) However, in our present study cognitive functioning expressed in IQ demonstrated moderate relation with competence. As cognitive development is far more extensive than IQ,

age might constitute a more accurate parameter for measuring cognitive development than IQ. However, high intelligence in young children who are generally not accorded the presumption of competence may be a reason to doubt incompetence and require individual competence assessment, which could be accomplished by using the MacCAT-CR.

Against our expectations, experience with disease and prior trial participation did not show to contribute to competence in this study. Although some authors describe that children with personal experiences of illness can obtain greater insight and understanding than children of comparable age without these conditions,(22) others argue that children with chronic medical disorders or life-threatening diseases might experience more difficulties in adaptation, social integration, treatment adherence, and development of autonomy than children without these conditions,(135;136) One possible explanation of our findings is that these effects outweigh each other.

Complexity and risk of the decision did not demonstrate impact on competence classification, although most authors agree that decisions concerning higher potential risk and more complexity frequently require a higher level of competence.(22) To illustrate the variance in complexity and risk between research procedures in our study: all oncology studies, a study that required anorectal manometry and a study that carried the risk of evoking an anaphylactic reaction were classified as high; a study that compared virtual asthma clinic consults with actual clinic visits in children with asthma and a study on use of an e-haler to improve medication adherence in asthma was classified as low; and in the middle category were studies with at least use of a placebo. We consider that providing a clear explanation of the research procedures might counteract the impact of the level of risk and the complexity of the research on children's competence.

The finding that SES and ethnicity did not demonstrate associations with competence indicates that generalizability of competence studies in populations of different ethnicity and SES might be possible.

Judgments of incompetence by parents frequently coincided with the MacCAT-CR incompetent classification, however parents' judgments of competence showed moderate agreement with the MacCAT-CR standard; parents judge their children more easily competent. In literature the opposite was described: in a sample of 120 young people undergoing orthopedic surgery in 1993, health professionals recommended much lower mean age for competence than parents did (10.3 vs 13.9).(137) Although study populations were different, parents' view on their children's competence might have shifted over the last two decades. Our results show that parents express a high expectation regarding their children's competence, allotting them more voice and responsibility.

Or articulated contrariwise, professional standards might be more precautionary than parents' judgments in children's competence assessment.

Limitations

The study design lacked a group of healthy children serving as controls volunteering for research participation, because in the Netherlands under current law they are not allowed to participate. Including healthy controls for competence assessment in a hypothetical trial would not allow for full assessment of capacities including appreciation. Because of this, comparisons between groups of diseased children and healthy children was not possible.

Another limitation may be caused by the decision to combine studies into low, middle or high classifications of complexity and risk. Safety regulation warrant no more than minimal risk for children in research. However, we supposed the decision on research participation to be weightier in more seriously diseased children like in oncology so we classified those in the high category, together with subjectively disagreeable research procedures, and with more complicated procedures. Unfortunately levels of risk and complexity are not yet well defined or quantifiable.(14;17) The same limitation is valid for combining trial experience and duration of illness. Both familiarity with having a chronic disease as well as prior research participation are supposed to add to the child's experience, but levels of experience are not well defined in literature either.

Conclusion, implications and future directives

The demonstrated major role of age determining children's competence to consent to clinical research, together with the previously estimated age limits for children's competence to consent, provide scientific underpinnings for proposals to modify the regulations regarding children's consent. As age limits for asking children's consent vary considerably between countries,(102) possible practical implications of this study's results need to be considered, taking into account the ethical and legal aspects (unpublished manuscript, September 2014, IH, PT, GM, MdV, JvG, RJL). The fact that parents generally have the authority to raise their children, providing them with rights and responsibilities, requires an equable consideration between the legal position of the child and that of the parents which need to be elaborated (unpublished manuscript, September 2014, IH, PT, GM, MdV, JvG, RJL). Future research is needed to examine children's competence to consent in the treatment context.

7 Assessing children's competence to consent to treatment

Irma M. Hein, Pieter W. Troost, Robert Lindeboom, Imke Christiaans, Thomas Grisso, Johannes B. van Goudoever, Ramón J.L. Lindauer
Submitted

Abstract

Objective

Knowledge on children's competence to consent to medical treatment is limited to date. Also, age limits for asking children's consent vary considerably between countries. The correlation between children's decision-making competence and age has never been systematically investigated. Decision-making on predictive genetic testing (PGT) is especially complicated, considering the ethical debate of the appropriateness of PGT in children. In order to examine just age limits for alleged competence to consent in children, we examined a standardized assessment tool, and investigated cutoff ages for children's competence to consent to PGT.

Methods

Participants were 17 pediatric outpatients between 6 and 18 years at risk for an autosomal

dominantly inherited cardiac disease, eligible for predictive genetic testing. The reference

standard for competence was established by experts trained in the four relevant criteria for competent decision-making (understanding, appreciation, reasoning, and expressing a choice). The MacArthur Competence Assessment Tool for Treatment (MacCAT-T) modified for children served as index test. Data analysis included raw agreement between different raters within the reference standard and the MacCAT-T classifications, and between the reference standard and the MacCAT-T competence classifications. The difference in mean ages between competent and incompetent children was tested, as well as inter-rater agreement for the MacCAT-T scores, and best discriminating cutoff ages for competence on the reference standard.

Results

Twelve (71%) children were competent by the reference standard, and 16 (94%) by the MacCAT-T, with an overall agreement of 76%. The expert judgments disagreed in most cases, the MacCAT-T judgments agreed in 65%. Mean age of incompetent children was 9.3 years and of competent children 12.1 years ($p = .035$). With 90% sensitivity, children younger than 10.0 years were incompetent, with 90% specificity children older than 11.8 years were competent.

Conclusion

Study results confirm feasibility of the MacCAT-T in children, and support the need for standardization of children's competence assessment. Findings on age cutoffs are, although premature, indicative for the competence of children between the age of 12 and 18 to be involved in the informed consent process. Future research on appropriate age-limits for children's alleged competence to consent is needed.

Introduction

Children from families in which a causative mutation has been identified for autosomal dominantly inherited cardiac diseases may be offered predictive genetic testing (PGT) at an age when cardiologic surveillance and preventive treatment are indicated.(138) In most cases the manifestations of these cardiogenetic diseases and in particular sudden death can effectively be postponed or prevented with lifestyle modifications, devices like an internal defibrillator or pacemaker, or use of medication.(139) There is some preliminary evidence that such interventions might reduce risk in children.(140) However, the penetrance of the mutations is variable and incomplete. For instance, approximately 50% of the mutation carriers of LQTS will develop symptoms.(141) PGT is generally considered acceptable, and it can identify individuals at increased risk of or in the early stage of a disease at a time when intervention can reduce the risk of morbidity and mortality. However, many ethical issues have arisen as a result of screening, and the ongoing debate indicates that the matter is complex and various pro's and con's illustrate individual cases.(138) This article does not address the larger important ethical questions of the appropriateness of PGT in children generally. Nevertheless, the ethical debate underlines the complexity of the issue and consequently the complexity of the individual's decision on PGT.

To illustrate the impact that cardiogenetic diseases might have, we will briefly describe the 5 syndromes dealt with in this article. Long QT syndrome (LQTS) is characterized by a prolongation of the corrected QT-interval on the electrocardiogram (ECG) and may lead to palpitations, dizziness, fainting, seizure-like fits and sudden death. Symptoms can be triggered by exertion, emotions, and loud noises in LQTS type 1 and 2, and can occur at rest in LQTS type 3. Manifestations of the symptoms can develop at all ages, but especially in LQTS type 1 and 2 occur in childhood.(139) Hypertrophic cardiomyopathy (HCM) is characterized by unexplained ventricular hypertrophy and is the most common cause of sudden unexpected cardiac death in young adults, particularly in competitive athletes. Other symptoms of HCM are dyspnea, chest pain, syncope, arrhythmias, thrombo-embolic events, and heart failure.(139) Brugada syndrome (BS) is a disease with typical abnormalities on the ECG and an elevated risk of sudden cardiac death. Fever as well as certain drugs can evoke the symptoms, most commonly seen in men around the age of 40.(142) Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a disease characterized by arrhythmias caused by a release of catecholamines in case of emotional upheaval, physical exercise or psychological stress.(143) The first symptoms can emerge in childhood or young adulthood. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disorder of the myocardium, that usually appears in adulthood, which increases the risk of an arrhythmia. It may not cause symptoms in its early stages, however, affected individuals may be at risk of sudden death, especially during strenuous exercise.(144)

When clinicians do believe testing is appropriate and provide testing to minors and their families, they will invite them to counsel about the disease and PGT and to give their consent to the suggested testing. This raises the question to what degree children understand the risks and benefits of PGT and the complexity of the decision, and can be deemed competent to give their consent. Informing children and gaining their cooperation has important advantages: answering questions and helping the child to understand what to expect will help the child to make sense of the experience, prevent misunderstanding or resentment, and increase compliance.(10) In addition, a just assessment of a child's competence to consent is vital for striking a proper balance in order to both protect children's interests when they are not fully able to do so themselves and to respect their autonomy when they are able to exercise it.

In medical practice, competence to consent is generally assessed implicitly and absent a standard. Clinicians tend to judge a child competent if the child's decision conforms to their own ideas of what was in the child's

best interest.(5) The reliability of unstructured competence assessments has been poor(145) and age standards prescribed by law are the guiding principle in clinician's competence assessments. Nevertheless, these legal age limits for deeming a child competent to consent vary widely between countries.(4) In Europe different domestic laws determine whether people are competent to consent to healthcare interventions.(11) Some countries consider autonomous decision-making lawful from the age of 18 onwards, and in other countries people are allowed to take healthcare decisions from a fixed age below legal majority, for instance, 12 years in the Netherlands and 15 years in Denmark(11). Most Canadian provinces and Switzerland apply a flexible system, stating that anyone who is capable can give informed consent, whereby competence is evaluated on a case-by-case basis.(11) In the United States, generally speaking, it often falls to parents or legal guardians to provide informed permission for medical decisions, and children under the age of 18 are to give assent,(126) meaning an affirmative agreement. In our study, in order to deal with discrepancies between the local law and international jurisdictions, we studied children's capacities for competent consent regardless of their age.

The competency of children to participate in medical decision making remains inconclusive and there is not a well-established assessment approach, neither have the legally set age limits been systematically investigated. Generally, the accepted standard in adults for assessing competence to consent consists of unstructured competence judgment by an expert, trained in the four criteria that reflect the standards for competence in most jurisdictions: understanding, reasoning, appreciation, and expressing a choice.(26)

Empirical studies on children's competence to consent to treatment are very limited. As far as we know, only 3 studies have been conducted using a structured instrument that addresses all four relevant criteria, which in all cases was the MacArthur Competence Assessment Tool for Treatment (MacCAT-T).(35) Chenneville investigated the MacCAT-T in a sample of youth with an average age of 17 years, with HIV.(146) A limitation of this study is that previously established cutoff scores were used,(147) which were established in a population of adult psychiatric patients and not evaluated in a sample of minors. Turrell and colleagues used the MacCAT-T in a comparative study on competence to consent in adolescents with anorexia nervosa and healthy controls and found group differences: adolescents with anorexia nervosa tended to experience more problems in reasoning about treatment than healthy controls.(27) Schachter and colleagues assessed understanding by means of a modified version of the understanding section

of MacCAT-T. Results suggested that the majority of adolescents with ADHD have an understanding similar to that of their parents.(148) None of these studies tested the reliability and validity of the structured assessment instrument against a reference standard. Empirical research on children's competence to consent is still a novel area.

Therefore, the aim of our study is estimating accuracy of a standardized competence assessment tool for children by modifying the MacCAT-T(35) for use in children and investigating cutoff ages for competence to consent in PGT.

Methods

Participants

Participants were pediatric outpatients between 6 and 18 years of age visiting the clinical genetics department at the Academic Medical Center in Amsterdam, the Netherlands, who were prospectively enrolled. They were referred by physicians for being at risk for an autosomal dominantly inherited cardiac disease. Exclusion criterion was not speaking Dutch. The study protocol was approved by the institutional review board and written informed consent was obtained from adolescents of twelve years and above and a parent or legal guardian before enrollment.

Competence assessment

As the index test for competence assessment we used the MacCAT-T, developed by Grisso and Appelbaum in 1998.(35) PGT in fact concerns diagnostic testing, however it takes place in a treatment context and therefore the MacCAT-T is the most appropriate instrument. The MacCAT-T measures the four aspects of decision-making capacities by operationalizing the four criteria into a semi-structured interview format: (1) understanding the disclosed information about the nature of the disease and the proposed intervention; (2) reasoning in the process of deciding about the proposed intervention, with a focus on abilities to compare alternatives in the light of their consequences; (3) appreciation of the effects of the intervention (or failure to undergo the intervention) on patient's own situation; and (4) expressing a choice about the intervention. Information disclosure required for informed consent is combined with an assessment of the patient's capacities. In this study the information disclosure was adapted to the specific cardiogenetic disease that a participant was tested for. The method provides scores for each subscale: 0-6 for understanding, 0-4 for appreciation, 0-6 for reasoning, and 0-2 for expressing a choice. The method does not offer a total

score or a cut off for competence, but the scores on the subscales need to be weighed by the interviewer. The MacCAT-T takes approximately fifteen minutes administration time. It receives empirical support in adult populations of mentally compromised patients.(26) The MacCAT-T was translated in Dutch, and translated back in English, by a professional translator. The version used was approved by the original author (T.G.). The Dutch version was modified for children which included the use of simple language to be understood by children of elementary school age. The interview was read out aloud to participants to exclude interference of children's reading levels. Furthermore, in the child version of the MacCAT-T we added questions on the influence of social relationships.(4) In the reasoning domain, "How do you think your parents will feel about you deciding to have this diagnostic test or deciding not to have it? And how do you think your friends will feel about it?" has been added (proprietary issues preclude publication of the version used).

Although a gold standard for competence does not exist, we will examine whether using a structured assessment instrument instead of an expert judgment would be possible without compromising accuracy. Usually, agreement is poor between unstructured clinical competence judgments, and often no better than chance.(26) Providing clinicians with information regarding the legal standards improves their judgments and significantly increases the inter-rater agreement.(26) These legal standards embody the four capacities: to communicate a choice, to understand the relevant information, to appreciate the medical consequences of the situation, and to reason about treatment choices. Clinicians aware of these relevant criteria are generally considered to establish the reference standard.(26) However, limitations of this approach may include discordance of expert competence judgments, leading to inconsistencies in the reference standard. Thus, poor performance of the MacCAT-T could either result from imperfections in the reference standard, or from an inaccurate assessment of competence based on the MacCAT-T.

Procedure

Children and parents were informed by a genetic counselor or clinical geneticist on PGT.(149) This conversation included issues necessary for informed decision-making comprising the aims, opportunities, and possible drawbacks of PGT. Parent(s) and children were asked if they consented to PGT. This conversation was videotaped and served as the basis for establishing the reference standard (see below). Usually at the same day, at most within 2 weeks, an interviewer from a panel of experts (listed below)

administered a MacCAT-T interview to the child. This interview was also videotaped, and rated afterwards.

The panel of 7 experts (including I.M.H., P.W.T., I.C., and R.J.L.L.) consisted of a clinical geneticist, child psychiatrists, child psychologists, and a social worker. The experts were trained in judging competence to consent by the 4 relevant criteria, and jointly practiced through rating 3 videos of the conventional informed consent conversation. In addition, the experts were instructed on rating the MacCAT-T, and practiced together by rating 2 videos of MacCAT-T interviews. Next, each member of the panel independently rated a number of conventional informed consent conversation videos and a number of MacCAT-T interview videos that were presented in random order and reciprocally blinded. Each MacCAT-T interview video was rated by 3 different experts. For all videos, the experts gave their judgment consisting of 1 of the following 4 categories: very likely competent, probably competent, probably incompetent, and very likely incompetent. We considered competence to be present when an expert gave a judgment of very likely or probably competent. The experts were not informed about the age of the children. For establishing the reference standard, each video from the conventional informed consent conversation was rated by 2 different experts, and also the clinical geneticist gave his/her judgment of the child's competence, adding up to 3 judgments.

The cognitive level of the children was assessed by the Wechsler Nonverbal Scale of Ability short version (WNV). The WNV is a clinical instrument for examining cognitive capacities of children and adolescents aged 4 to 21, which is suitable for the general population as well as for children with cultural, linguistic, educational or socio-economic varying backgrounds. The subtests do not invoke verbal capacities as instructions are made by pictograms, and the validity and reliability of the short version are good. The WNV was administered by trained certified professionals (special education or psychology graduates) under supervision of a senior professional.

Analysis

Competence was considered present when at least 2 out of 3 judgments were positive, for both the expert judgments establishing the reference standard, and the ratings based on the MacCAT-T. Agreement between the reference standard and the MacCAT-T based competence classification (accuracy of the MacCAT-T competence classifications) was expressed as the raw percentage agreement.

Reproducibility of the MacCAT-T total and subscale sum scores as obtained by 3 ratings on the MacCAT-T, was estimated using intraclass correlation coefficients (ICC, model 1, single measure).

Agreement between the 3 ratings of the experts, and between the 3 ratings based on the MacCAT-T, was expressed as the raw percentage.

Independent samples t-test was used to test the difference in mean ages between competent and incompetent children on the reference standard. Best discriminating cutoff ages for competence on the reference standard were estimated using receiver operator characteristic curve (ROC) analysis, with area under the curve (AUC) exceeding .70 considered adequate for the estimation of age cutoff.

Results

Between January 1, 2013 and January 1, 2014, 23 children were eligible. Of them, 6 did not participate for different reasons, concerning time constraints in 2 cases, elevated stress in 2 cases, and no clear reason in 2 cases. Non-participants were 4 males, mean age 10 years, and 2 females, mean age 12 years. The characteristics of the 17 included children are listed in table 5. The age range of the participants was between 6 and 17, mean 10.9, variance 6.7. The Intelligence Quotient as measured by the WNV ranged from 89 to 126, with a mean of 107.5.

By the reference standard 12 (71%) children were classified competent, by MacCAT-T classification 16 (94%) children. In 24% of the children, the expert raters classified the child as incompetent and the MACAT-T based rating did not. The other way around did not occur. Overall agreement was 76%.

MacCAT-T total scores inter-rater agreement coefficient was .95. Inter-rater agreement on subscale scores were .93 for understanding, .91 for appreciation, .91 for reasoning and total agreement for choice.

Agreement between all 3 ratings on the reference standard occurred in 8 cases (47%), and on the MacCAT-T based classification the 3 ratings showed agreement in 11 cases (65%).

On the reference standard, mean age of incompetent children was 9.3 years and of competent children 12.1 years ($p = .035$).

Age as a predictor of competence on the reference standard showed AUC .80 (95%; .55 – 1.00). Cutoff age for competence with 90% sensitivity was 10.0 years and with 90% specificity 11.8 years.

Table 5. Baseline characteristics and outcomes of competence classifications on reference standard and MacCAT-T

Child no.	Disease tested for[a]	Age in years (Male/ Female)	Expert classification (Competent: Incompetent)	MacCAT-T score, (subscale scores U/A/R/C)[b]	MacCAT-T classification (Competent: Incompetent)
1	HCM	6 F	I (0:3)	29 (21/2/3/2)	C (2:1)
2	LQTS	7 M	I (0:3)	30 (21/4/4/2)	I (1:2)
3	BS	9 M	I (0:3)	36 (23/4/7/2)	C (3:0)
4	HCM	9 M	C (3:0)	32 (18/4/8/2)	C (3:0)
5	HCM	10 M	C (2:1)	31 (21/4/4/2)	C (2:1)
6	HCM	10 M	C (2:1)	35 (22/4/7/2)	C (3:0)
7	HCM	10 F	C (3:0)	38 (25/3/8/2)	C (3:0)
8	HCM	10 F	C (2:1)	36 (23/2/9/2)	C (3:0)
9	HCM	11 M	C (2:1)	36 (22/4/8/2)	C (3:0)
10	HCM	11 F	I (1:2)	29 (18/2/7/2)	C (2:1)
11	HCM	11 M	I (1:2)	38 (25/4/7/2)	C (3:0)
12	HCM	12 M	C (2:1)	30 (20/4/4/2)	C (2:1)
13	CPVT	12 M	C (2:1)	38 (24/4/8/2)	C (3:0)
14	CPVT	13 F	C (2:1)	34 (24/3/5/2)	C (2:1)
15	LQTS	13 F	C (3:0)	40 (25/4/8/2)	C (3:0)
16	ARVC	14 F	C (3:0)	40 (26/4/8/2)	C (3:0)
17	ARVC	17 M	C (3:0)	38 (25/4/7/2)	C (3:0)
					76% agreement MacCAT-T vs expert

[a] ARCV = arrhythmogenic right ventricular cardiomyopathy, BS = Brugada syndrome, CPVT = catecholaminergic polymorphic ventricular tachycardia, HCM = hypertrophic cardiomyopathy, LQTS = long QT syndrome.
[b] Mean scores from three raters, U = Understanding, A = Appreciation, R = Reasoning, C = Choice

Discussion

Results of the current study show initial indications for reliability and validity of the MacCAT-T in children eligible for PGT: inter-rater agreement on scores was high, and agreement between MacCAT-T based competence classifications and the reference standard was adequate, although not decisive. By using the MacCAT-T, children were more easily classified as competent than by the reference standard.

Age cutoffs for presumed competence to consent to PGT in this sample, based on the reference standard, were: children of 11.8 years and above were very likely to be competent to consent to PGT, and children of 10.0

years and younger were most probably not competent to consent. Earlier work showed that the modified MacArthur Competence Assessment Tool for Clinical Research was valid and reliable for use in children,(150) and in a population of 161 pediatric patients eligible for research participation, children older than 11.2 years were generally found competent to consent and children younger than 9.2 years incompetent.(150) Obviously, children's competence to consent to treatment and their competence to consent to clinical research are not the same. It has been stated that consent to participation in research must be a more stringent process than consent to treatment, because the research participants are generally not asked to participate for their individual benefit, but to help improve general health care.(29) Nevertheless, the fact that the present findings are consistent with previously found age cutoffs in children regarding their competence to consent to clinical research, increases support for the results.

The rate of disagreement between the competence ratings was high, both for expert judgments and for the MacCAT-T judgments. Even so, where the expert judgments disagreed in most cases, the use of the MacCAT-T led to an increased agreement. Factors that explain the high rate of disagreement between judgments, no matter what assessment method was used, might be related to normative aspects and difficulties in assessing developmental aspects in children. Although decision-making competence may be a matter of minor differences,(30) the competence judgments require a definitive assessment of whether competence is present or not. It is still under debate whether a threshold for competence can be established based on the sum of the different decision-making capacities.(31) Especially in children, development of different domains relevant for competent decision-making may not occur simultaneously, which may complicate the assessment of a child's competence.

For the clinical practice of PGT, no definitive conclusions can be drawn from this study's results. Yet, the results indicate preliminarily that competence to consent to treatment can be present in children under the age of 18, even when it concerns a complex decision regarding PGT. Moreover, in our small sample, all children of 12 years and above were considered competent to consent to PGT, independent of the assessment method used. Taking into account that understanding of the relevant medical information is critical for competent decision-making, it deserves attention to supply even young children with adequate information tailored to their developmental stage and comprehension level,(4) in order to optimally involve them in the informed consent process.

Limitations

A salient limitation of this study concerns the small sample size and wide age range, which complicate an exhaustive analysis of the data. Furthermore, poor reliability among experts forming the reference standard is a significant limitation, as it was the benchmark that the MacCAT-T results were compared to. The fact that all but 1 child in the sample was rated as competent by using the MacCAT-T should be noted, as this could relate to limited utility when using the MacCAT-T. Although participants of a wide age range were recruited, the obtained sample contains for the greater part children between 9 and 14 years of age, thus the generalizability of the results beyond this age group must be considered with caution.

Conclusion

Our present results confirm that the MacCAT-T is promising for standardizing competence assessment in children in treatment situations. The strength for using the MacCAT-T includes high interrater agreement, and the consistency in MacCAT-T results compared to the expert judgments lends additional support to the use of the instrument. The reliability and validity of the MacCAT-T must be demonstrated in a larger sample of children. More extended research on children's competence to consent to treatment is needed, especially in pediatric populations where competence issues can become problematic. Examples of such situations comprise children older than the legal age for competence who refuse a recommended medical treatment, for instance children with anorexia nervosa who refuse tube feeding, or children with renal insufficiency who refuse dialysis. Also children younger than the legal age for competence who wish for a certain treatment, like children eligible for medical interventions for gender dysphoria, must be considered. More empirical research should provide objective data to underpin a just age limit for alleged competence to consent to treatment in children. In addition, an accurate assessment instrument is needed to substantiate competence judgment in individual cases.

8 Why do children decide not to participate in clinical research: a quantitative and qualitative study

Irma M. Hein; Pieter W. Troost; Martine C. de Vries; Catherijne A.J. Knibbe; Johannes B. van Goudoever; Ramón J.L. Lindauer
Accepted for publication, Pediatric Research

Abstract

Background

More pediatric drug trials are needed, but although specific pediatric regulations warrant safety, recruitment of children for these trials remains one of the main difficulties. Therefore we investigated potential determining factors of non-participation in clinical research, in order to optimize research participation of children by recommending improved recruitment strategies.

Methods

Between January 1, 2012 and January 1, 2014, we performed a prospective study among161 pediatric patients, aged 6 to 18 years, who were eligible for clinical research. We quantitatively analyzed the association of potential explanatory variables (e.g., age, cognitive development, experience, ethnicity) with non-participation and qualitatively analyzed interviews on reasons for non-participation.

Results

60% of the children did not participate in the research project on offer (39% decided not to participate, 21% were indecisive). Lower age, less disease experience, and less complex research with lower risk were predictive for not participating. Time constraint and extra burden were expressed as decisive reasons for not participating.

Conclusions

Strategies to optimize research participation should be aimed at younger children and their families, who are logistically challenged, and unfamiliar with health care and research. Recommendations include informing pediatric patients and their families of the value of research; minimizing logistic burdens; and improving accessibility.

Introduction

More drug research in children is needed, because currently 36-90% of drugs prescribed to children have not been tested in their age group.(151) Prescribers often have no alternative but to resort to off-label or unauthorized products, without having evidence-based information regarding drug effects on children to guide them and help them weigh the risks and benefits of the drug. Conducting more clinical research in children will mean an increased demand for children to participate. Evidently research with this vulnerable population involves many unique ethical and legal considerations which have led to the development of specific pediatric regulations and guidelines to warrant safety.

Research projects need approval at different levels before implementation. Legislative regulations in Europe and the United States mostly prescribe that pediatric research that does not offer participants a potential clinical benefit is only allowed when there is (minor increase over) minimal risk and minimal burden.(152) Research that may offer the participant potential benefit is assessed by weighing risks and burden against potential gain. Institutional review boards (IRBs) or research ethics committees (RECs) are charged with the assessment of the research protocols. Informed consent or assent is required from research subjects and their proxies. Regarding minors, parents are required to provide permission, while minors can provide assent or consent to biomedical research when appropriate.(24)

Significant difficulties occur in the recruitment for clinical research involving minors.(153) A recent study showed that less than half of the clinical research projects approved by the IRB succeeded in procuring 80% of confirmed participants at the planned closing date. While a consistent pattern of trial-characteristics associated with successful recruitment could not be identified,(154) previous studies show increasing evidence for the complexity that underpins adult participants' decisions to consent in research. Evidently, adults base their decision on a combination of practical

considerations, levels of interest, relational factors and more general values like a sense of responsibility to contribute knowledge to the community.(155)

At present, empirical evidence on what children and parents conceive as burdensome and what they appreciate in research participation is limited. Reasons for, or against, participation may be influenced by ethnic status, societal factors and anxiety or stress, and concrete barriers such as time commitment, childcare and transportation difficulties.(156) Providing participants with inadequate information concerning the particulars of the research also interferes with the participants' ability to make well-considered decisions.(157) Studies in adolescents, one of which concerned a hypothetical research project, demonstrated that several participants expected direct health benefit from being questioned and examined by the physician,(158-160) a main reason for participation was charity(161) and half of a the eligible subjects refused for no apparent reason.(162) Sample sizes of the studies are small, children under twelve are underrepresented, and studies do not show results for subdivisions of children in different age groups. Furthermore, answers of children might be biased by social desirability. Combining qualitative and quantitative outcomes can offer a more comprehensive insight into factors that promote participation as well as factors that militate against it.

Insight into motives and characteristics of children who decide not to participate in research is of importance for the development of strategies to improve recruitment rates and by that increase successful conduct of research. The aim of our study was (1) to quantitatively investigate potential determining factors for children's non-participation and to what extent these contributed to the decision-making process; and (2) to qualitatively investigate children's subjective reasons for non-participation across different age spans.

Method

Participants

The population for this study consisted of participants in a large study on competence to give informed consent in children, which is described comprehensively elsewhere.(4) Between January 1, 2012 and January 1, 2014, this population of 161 pediatric patients, aged 6 to 18 years, eligible for real-life clinical research participation were prospectively recruited at inpatient and outpatient clinics in Amsterdam, Rotterdam and The Hague.(133) The clinical research projects consisted of ten randomized controlled trials and three observational studies at departments of pediatric

oncology, pediatric gastroenterology, internal medicine, ophthalmology and pulmonary diseases. Only non-native Dutch speakers were excluded from research participation.

For the quantitative study all subjects were included, for the qualitative study a sample consisting of every first enrolled participant of each elected age group (8-16) of each of the 10 research projects was selected, which would allow to aggregate sufficient data for analysis.

The study procedures were judged and approved by the IRBs of the participating institutions. Prior written informed consent was obtained from minors aged 12 and older and their parents.

Assessment method

1. Quantitative

Next to demographic data, we collected measures of potential determining factors: age; gender; experience, expressed in the number of trials previously participated in and duration of disease (low: no prior trial participation and duration of disease less than one month, moderate: no prior trial participation and duration of disease more than, or equal to, one month, high: prior trial experience); socio-economic status (SES), indicated by the level of education of the highest educated parent (low: no primary school, primary school, special primary school, special secondary school, middle: preparatory education, secondary vocational education, senior general secondary school, preparatory scientific education, high: college, university); complexity and risk of the research procedure (low: no risk, no blinding, moderate: little risk, placebo, and blinding, high: possible risk, complex or disagreeable research procedure, serious disease, placebo, and blinding); intelligence quotient (IQ), assessed by the Wechsler Nonverbal Scale of Ability, short version administered by trained certified professionals (low: under 90, average: 90-110, high: 110 or higher); and ethnicity (Western European, Middle East, Surinam/Antillean or other). We used the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) modified for children, (4;150) and a semi-structured interview format to assess children's decision-making competence concerning research participation. We also asked the parents to assess their own children's decision-making competence concerning research participation. Finally, we collected the child's own decision on participation in the research project on offer.

2. Qualitative

The MacCAT-CR understanding section disclosed information and provided questions on the children's comprehension of the purpose of the

clinical research, the duration, the procedures, the research objectives, blinding in different treatment arms and the possibility of receiving placebo, and possible risks and benefits. The MacCAT-CR reasoning section contained questions on children's thoughts about research participation: what would you rather do, participate or not?; why would you rather participate, or not participate?; what do you think is good about participating, and what is not good about it?; why would you prefer participating (or not participating) above not participating (or participating)?

Data analysis

1. Quantitative

We used multiple logistic regression analysis to examine to what extent the possible explanatory variables – age, gender, disease experience, SES, complexity and risk of the study, intelligence, ethnicity, decision-making competence and parental competence judgment – were related to the decision to participate, or not participate, in the research project. First we examined the distribution of these variables in the sample in contingency tables. Ethnicity classifications were collapsed into Western European and other ethnicity. Then, all explanatory variables were entered simultaneously into the model to examine which variable contributed most to the probability for a positive decision on trial participation. Since adjusted odds ratio for the variables depend on their scale of measurement, we used the Wald-statistic as a measure of strength of the association with trial participation.

Calibration of the model was examined using the procedure of Hosmer and Lemeshow(129) (HL) to test the differences between expected model probabilities and observed probabilities of the decision to participate in research. A HL-test p-value > .05 indicates no statistically significant differences between observed and expected frequencies regarding the decision to participate in research and thus the model fits acceptably. Accuracy of the model was examined by a receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) served as the validity coefficient; AUCs exceeding .70 are generally considered adequate.

2. Qualitative

The interviews were transcribed verbatim and checked against the recordings. We used the software package MAXQDA to manage data. Two researchers (Lotte Gelens, IH) read and annotated five transcripts independently with no predetermined coding structure. We compared the transcripts to identify emergent themes and to identify initial codes.

Further discussion identified predominant themes. The codes agreed upon were: reasons to participate; expected benefit; reasons not to participate; expected burdens; decisive reason; personal beliefs; probable choice; therapeutic misconception (conceptualizing research as treatment); and expected impact of participation. Each researcher then coded the remaining transcripts, while looking for consistencies to increase trustworthiness within and between transcripts. To illustrate the interviewees' responses, we extracted some common considerations mentioned by the participants that will be presented in the results section below.

Results

1. Quantitative study

Baseline characteristics

As the characteristics of the study participants were described elsewhere,(133) we only give a brief overview here: of 209 children eligible for this study, 161 were enrolled, mean age 10.6 years (age range: 6-18).

Association of variables with participation

The distribution of the variables in contingency tables are demonstrated in Table 6. Sixty two children (39%) decided not to participate, 34 (21%) did not make a decision on participation in the research project for which they were approached, and 64 children (40%) decided to participate. Higher age, higher SES, higher complexity and risk of the research procedure, Western ethnicity and decision-making competence showed a positive association with the decision to participate ($P<0.01$).

Strength of associations

The relative contribution of each characteristic to the probability of the decision to participate in research is listed in Table 7. High complexity and risk had the highest Wald statistic (13.6) and was most predictive for a decision to participate. Furthermore, greater disease and trial experience and a higher age contributed to a positive decision on trial participation (Wald statistic low experience 8.5, high experience 6.7, age 5.7). The Hosmer and Lemeshow goodness of fit p-value was: $p=.24$. There were small differences between expected model probabilities and observed probabilities for the decision to participate (overall correct > 76%).

Table 6. Distribution of variables among children who participate and children who do not

	Total (N=161)	Participation (n= 64)	No decision or no participation (n= 97)	Odds ratio (95% CI)	P
Mean age in years (SD)	10.6 (2.8)	11.4 (3.3)	10.1 (2.2)		<0.01
Male, N(%)	76 (47)	30 (47)	47 (47)	1.0 (0.54-1.93)	
Disease experience, N(%)					
Low*	49 (30)	18 (28)	31 (32)	1.00	
Medium	74 (46)	24 (38)	50 (52)	0.83 (0.39-1.77)	0.62
High	38 (24)	22 (34)	16 (17)	2.37 (1.00-5.64)	0.51
SES, N (%)					
Low*	18 (11)	2 (3)	16 (17)	1.00	
Middle	76 (47)	27 (42)	49 (51)	4.41 (0.94-20.63)	0.60
High	67 (42)	35 (55)	32 (33)	8.75 (1.86-41.01)	<0.01
Complexity and risk, N (%)					
Low*	29 (18)	28 (44)	1 (1)	1.00	
Moderate*	113 (70)	20 (31)	93 (96)	1.00	
High	19 (20)	16 (25)	3 (3)	10.44 (2.90-37.61)	<0.01
IQ, N (%)					
Low*	52 (32)	15 (23)	37 (38)	1.00	
Average	66 (41)	29 (45)	37 (38)	1.93 (0.89-4.19)	0.09
High	43 (27)	20 (31)	23 (24)	2.15 (0.92 -5.02)	0.08
Ethnicity, N (%)					
Western-Europe*	91 (56)	49 (77)	45 (46)	1.00	
Other[1]	70 (44)	15 (23)	52(54)	0.23 (0.12-0.47)	<0.01
Parental competence judgment					
Incompetent*	34 (21)	11 (17)	23 (24)	1.00	
Competent	125 (79)	53 (83)	72 (76)	1.54 (0.69-3.43)	0.29
Competent to decide					
No	34 (21)	16 (25)	45 (46)	1.00	
Yes	125 (79)	48 (47)	52 (54)	2.60 (1.23-5.29)	<0.01

*(Combined) reference category

1) Other: Middle East (30%), Surinam/Antilles (13%) and "other"(1%)

Table 7. Association of variables with research participation

	B	Wald	Corrected Odds Ratio (95% CI)
Age	0.24	5.67	1.3 (1.0-1.5)
Gender	0.20	0.22	1.2 (0.5-2.8)
Disease experience			
Low*	0	8.52	0
Medium	0.14	0.09	1.1 (0.5-2.9)
High	1.43	6.66	4.2 (1.4-12.3)
SES			
Low*	0	2.37	0
Middle	1.00	1.07	2.7 (0.4-17.8)
High	1.52	2.12	4.5 (0.6-34.9)
Complexity and risk			
Low*	0	0	0
Moderate*	0	0	0
High	2.81	13.60	16.8 (3.7-75.2)
IQ			
Low*	0	0.45	0
Average	0.25	0.21	1.3 (0.5-3.6)
High	0.41	0.45	1.5 (0.5-4.9)
Ethnicity			
Western*	0	0	0
Other	-0.54	1.14	0.6 (0.2-1.6)
Parental competence judgment			
Incompetent*	0	0	0
Competent	-0.16	0.06	0.9 (0.2-3.1)
Competent to decide			
No*	0	0	0
Yes	0.28	0.23	1.3 (0.4-4.1)

*(Combined) reference category

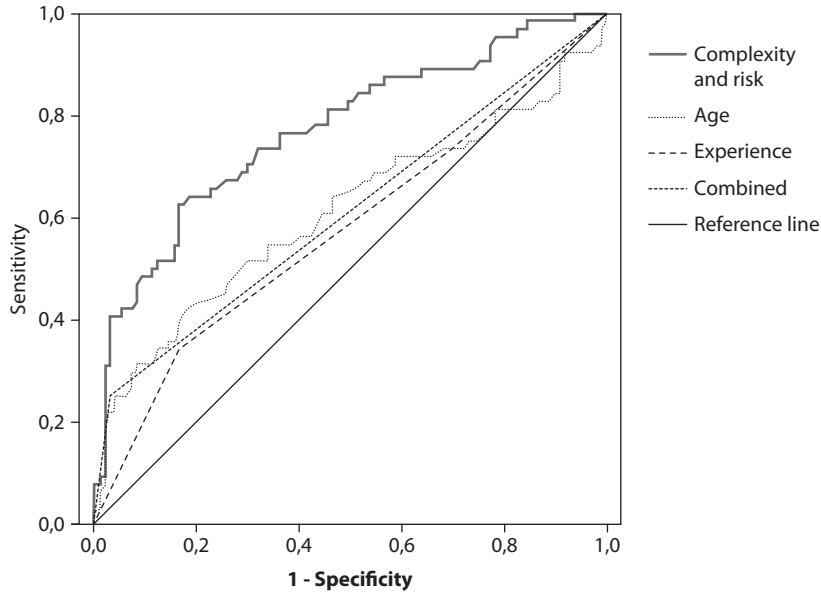
Accuracy of associated variables

We further examined the predictive value of explanatory variables using AUC as a measure of accuracy: complexity and risk of the research procedure had an AUC of .61 (95% CI .52-.70); age .61 (95% CI .51-.70); disease experience .58 (.48 -.67). The AUC of all three explanatory variables combined in the model was .77 (95% CI .69-.85) (Figure 5).

2. Qualitative study

Thirty-five children were included in the qualitative study: mean age 11.9 years, SD 2.45, age range: 8-16. In this subsample 25 children (71%) decided to participate in the clinical research on offer, meaning there was

Figure 5. ROC curves of factors predictive for a decision to participate in research



a sample bias (40% of the total population decided to participate, 71% of the subsample).

Reasons for not participating

Children aged 9 and above presented 18 reasons for not participating in research. These reasons related to expected burdens for themselves directly deriving form research procedures, such as extra time investment, possible adverse effects of trial medication, or the inconvenience of sitting still. In 7 cases, these reasons were decisive for children not to participate. Children aged 8 did not express any reasons for not participating.

Several children all aged 9 and above expressed 10 collateral burdens pertaining to themselves. No child explicitly mentioned a collateral burden for others. Many children mentioned that participating would impact on their time-schedule, and children of all ages mentioned they did not want to miss school. Personal beliefs for not participating were expressed by children of 10 years and older. Some children simply expressed they did not feel like participating.

Reasons for participating

On 40 occasions, children mentioned that participation would benefit others, some children expressed this more than once. To help advance

knowledge for physicians was mentioned 3 times. Helping others was mentioned by children of all ages; in children aged 10 and above, helping others was frequently the decisive reason for participation.

In 11 cases, children, aged 8 to 13, mistook trial participation for individualized treatment. Children older than 13 did not express such a direct benefit. An example of an 11-year old asked to participate in research on treatment methods for functional abdominal pain clearly shows the child's misconception of the trial's purpose:

Interviewer: "Why would you rather take part?
Child: "Well, because the doctor told me there is an 80% chance that you succeed with the therapist, and… Yes, I really want my stomach ache to go away."

Only 2 children, an 8 and 16-year old, correctly interpreted the direct benefits they would receive from participating in the research. The following quote by the 16-year old particpating in a study in gastroenterology illustrates this perfectly:

Interviewer: "Why would you rather take part?"
Child: "Well, maybe they can find a solution for it that, yeah… mainly generally. And in the end maybe for me too."

Eight children of 10 years and above mentioned collateral benefits for themselves, including the participation experience, which they considered fun, interesting and instructive; however, younger children failed to mention these kind of motives altogether. Children of all ages expressed the belief that the research would not cause them any harm as a reason for them to participate. Personal beliefs concerning trial participation were mentioned by children of all ages (21): common responses were, "I did it before," "it is your own choice," "I signed already, it is safe."

Discussion

The quantitative study on potential determining factors for children's research participation showed that a lower age, less experience with disease and research, and less complex decisions with lower risk were all decisive factors not to participate in research. The percentage of non-participation was 60%, of which 39% decided not to participate, while 21% remained indecisive. Although these results are solely based on the child's decision – in children under the age of 12, the parent's decision would be decisive – this percentage of non-participation is remarkably high. Research procedures in

this study with more complexity and a higher level of risk were performed in pediatric oncology, and one study in gastroenterology. The outcomes of prior studies are similar to our findings.(153) Possible explanations for the higher participation rate in these cases point to the fact that families with health care experience may be more willing to allow their child to be enrolled in research. Furthermore, a conceivable motivation of seriously ill children to participate in research may be their higher dependence on the health care system and their search for hope. Moreover, children who had previously participated in studies, or families who were well-informed about pediatric studies by active patient associations were more willing to participate.(153) Thus familiarity may be an important factor in the decision on research participation.

Less willingness to participate amongst younger children may not be surprising. In previous studies, parents expressed that a restricted understanding of a study and its regulations was an important factor in deciding not to have their child participate in the study.(153) Younger children may be equally discouraged if they do not fully understand the impact of the decision to participate in a study. Information provision directed at parents, and clear, age-appropriate information for children may then help to improve the willingness to participate. Another factor may be that parents raising young children can feel overwhelmed, particularly when their child is sick. Minimizing the burden of research procedures in practical ways, for instance by promoting online visits and telephone interviews instead of outpatient visits, might help relieve some of the pressure.

The other examined factors; gender, SES, intelligence, ethnicity, and parental judgment of a child's competence to consent did not contribute significantly to promote or decline research participation.

The qualitative study on reasons that promote or discourage research participation expressed by children of different ages demonstrated that time constraints and direct burdens from the research procedures, such as waiting, sitting still, or extra tests, were the main reasons for not participating for children of 9 years and older. Research procedures that were considered burdensome by children varied between individuals. In our sample there were no trial procedures that required extra vena punctures or lumbar punctures – procedures involved electroencephalography, electrocardiography, magnetic resonance imaging, extra medication, diaries, and anorectal manometry. In general, children older than 9 years were able to clearly convey their assessment on burdens and benefits.

Altruism was a main reason for children of 10 years and older to participate in research. This corresponds to findings in the adult population.(163)

Another main reason was that children mistook research for individual treatment and expected health gain from participating in the research. This therapeutic misconception was prevalent in the population of children under 13, but not in late adolescents. In adults, therapeutic misconception emerged as a major theme,(163) in previous studies in children it was prevalent as well.(160) Thus in children, understanding of the purpose of clinical research relies heavily on the provision of information, which should be tailored to their comprehension level.(4) Although children in our sample were well-informed about the purpose of the research, including an explanation of the difference between therapeutic goals and research goals, younger children and early adolescents showed difficulties understanding.

The results of both the qualitative and quantitative study show that the motives and characteristics of children who decide not to participate are the following: younger age, unfamiliar with health care and research, logistically challenged, not optimally informed and not fully aware of the societal benefits. Strategies to improve recruitment rates could be targeted especially at pediatric patients and their families who fall into these categories. An example of an effective strategy to increase awareness of shared societal responsibility for trial recruitment can be found in adult studies,(154) where public campaigns were recommended to convince professionals and the general public of the value of research for clinical practice. This included informing adult patients about the use of data to help future treatment and efforts to improve patient care.(154) These strategies might also prove effective with pediatric patients and their parents.

Strategies for decreasing the logistic burden for children and families may be aimed at improving accessibility; the burden of time constraint should be addressed and minimized. Furthermore, as the majority of children older than 9 years were able to convey their assessment on burdens and benefits in a clear way, it might be constructive to give children a voice in the assessment of what they experience as burdensome and valuable in research. An example is the Young Person's Advisory Board of the UK Medicines for Children Research Network (http://www.crn.nihr.ac.uk/children/pcpie/young-persons-advisory-group/), consisting of children, aged 8 to18 years, who have experienced medical conditions. The board involves these children and families in research and raises research awareness and motivation amongst young people. Expanding similar initiatives may contribute to improving pediatric research recruitment rates.

Limitations

The population of participants was a heterogeneous group, which may limit the generalizability of the results to specific populations of children. Furthermore, it is a limitation that the parental view and its possible impact on the child is not included in this study. Another limitation may be caused by the decision to combine studies into low, middle, or high classifications of complexity and risk. Safety regulation warrants no more than minor increase over minimal risk for children in research. However, we anticipated the decision on research participation to be weightier in more seriously diseased children like those with cancer, thus we classified those in the high category, together with subjectively disagreeable research procedures, and the more complicated procedures. Unfortunately levels of risk and complexity are not yet well defined or quantifiable.(14;17) The same limitation is valid for combining trial experience with duration of illness. Both familiarity with having a chronic disease as well as prior research participation are supposed to add to the child's experience, but such levels of experience are not well defined in literature either.

Finally, the role of the researcher fell outside the scope of this study. Researchers themselves, or the relationship between pediatric patients and researchers, might have specific characteristics that could increase or decrease the recruitment rate of studies.

Conclusion

Younger children, children with less disease experience, and children deciding on participation in less complex research with less risk, were more prone to decline research participation. Time constraints and direct burdens from the research procedures were the main reasons for not participating expressed by children of nine years and older. Altruism was a subjective reason for research participation in children aged ten to eighteen, and well-informed adolescents of 14 years and older were not subject to therapeutic misconceptions.

Unfamiliarity, limited information provision for parents and young children, and logistic burdens are factors that negatively affect research participation, therefore strategies should be aimed at these issues. Campaigns directed at convincing the professionals and general public of the value of research for clinical practice should include informing patients about the use of data and efforts to improve quality when entering the hospital. Logistic burdens should be minimized by coaching and guiding of children and parents; and by improving accessibility. Involving children and

families in advisory boards is a way to improve research awareness among eligible participants and to align research procedures with the participants' preferences.

Directives for future research include evaluation of the actual experience of research participation as well as research on how pediatric patients and their parents evaluate proportionality in decisions on research participation.

9 Informed consent instead of assent is appropriate in children from the age of twelve

Policy implications of new findings on children's decision-making competence in the clinical context

Irma M. Hein, Martine C. de Vries, Pieter W. Troost, Gerben Meynen, Johannes B. van Goudoever, Ramón J.L. Lindauer
Submitted

Abstract

Background

For many decades, the debate on children's competence to give informed consent in medical settings concentrated on ethical en legal aspects, with little empirical underpinnings. Recently, data from empirical research became available to advance the discussion. It was shown that children's competence to consent to clinical research could be accurately assessed by the modified MacArthur Competence Assessment Tool for Clinical Research. Age limits for children to be deemed competent to decide on research participation have been studied: generally children of 11.2 years and above were competent, while children of 9.6 years and younger were not. Age was pointed out to be the key determining factor in children's competence. In this article we reflect on policy implications of these findings, considering legal, ethical, developmental and clinical perspectives.

Discussion

Although assessment of children's competence has a normative character, ethics, law and clinical practice can benefit from research data. The findings may help to do justice to the capacities and challenges children may face when deciding about treatment and research options. We discuss advantages and drawbacks of standardized competence assessment in children on a case-by-case basis compared to application of a fixed age limit, and conclude that a selective implementation of case-by-case competence

assessment in specific populations is preferable. We recommend the implementation of age limits based on empirical evidence. Furthermore, we elaborate on a suitable model for informed consent involving children and parents that would do justice to developmental aspects of children and the specific characteristics of the parent-child dyad.

Background

In clinical practice an accurate assessment of children's decision-making competence is needed to avoid two pitfalls: to impose complex medical decisions on children who are unable to make them, and to inadvertently exclude capable children who want to take part in decision-making.(106) For many decades, the debate on children's competence to give informed consent or assent in medical settings concentrated around ethical and legal aspects, with little empirical underpinnings.(150) In clinical practice many questions remained unanswered, for example which age span to evaluate, how to study the full range of abilities relevant to children's decision-making described in the literature, how to assess decision-making capacities regarding different types of medical decisions, and how to objectively assess children's competence. Progress was hard to achieve in debates on the subject and the lack of consensus on children's competence to consent was reflected by the restricted clinical implementation of the concept. There was a gap between recommendations regarding policies for children's involvement in the consent procedure and what had been documented in scientific research about children's competence assessment. The empirical approach emerged as a designated way to examine the dilemmas.

Recently, objective data stemming from empirical research on children's competence to consent became available, offering an opportunity to further the discussion. Research demonstrated in a sample of 161 pediatric patients that children's competence to consent to clinical research could be assessed in a valid and reliable way by means of an instrument, the modified MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR).(150) In the same study, the four domains representing competence in most jurisdictions (understanding, appreciation, reasoning and expressing a choice) appeared to constitute a single trait or continuum of competence in children, which allowed for estimating a cutoff score on MacCAT-CR above which competence was likely. This is in contrast with adult literature, stating that scores on subscales need to be weighted independently, and that failure in one domain could translate into an

incompetent assessment.(3;35) In adults, because of this presumption, dimensionality was never tested.

Age limits for children to be deemed competent to decide on research participation were estimated: children of 11.2 years and above generally appeared to be competent, while children of 9.6 years and younger were not. Between 9.6 and 11.2 years, there was a change-over.(150) For treatment decisions, a preliminary study using MacArthur Competence Assessment Tool for Treatment (MacCAT-T) on decisions about predictive genetic testing, revealed that most children above the age of 11.8 were competent to consent.(134) The results from these studies in the research and in the treatment context show that MacCAT-scales modified for children are practicable in both settings and suggest that age-limits for competence align.

Furthermore age turned out to be the key determining factor in children's competence, with a small additional contribution of intelligence. Theoretical assumptions that risk and complexity of the decision would be related to a competence classification could not be confirmed with empirical data.(130) This demonstrated that more radical decisions, requiring a higher level of competence, could possibly be made by children as young as the group of children who were able to make lower impact decisions. An explanation might be that children at a certain age have the required capacities, and competent decision-making is possible when information provision is of good quality. For other potential determining factors for competence, like gender, systemic influences, disease experience, ethnicity and socio-economic status, no clear relationship with competence could be demonstrated either. Interestingly, parents appeared to judge their child more readily competent than experts would.(130)

These recent empirical findings do not stand alone however, and need to be considered in view of their context. Since the age limits for asking children's consent stated in many jurisdictions do not coincide with those demonstrated in our research,(150) we need to evaluate whether it would be advisable to reset local statutory age-limits. Having the possibility to assess children's competence individually in a standardized way, an alternative option (namely to let go of rigid age limits for alleged competence and switch to a case-by-case assessment) might be considered. For example, now that it is possible to establish a very intelligent eight-year old boy's competence, we need to consider if it would be judicious to do so and to allow him an independent consent. Although our assessment instrument proved to be accurate, there might be possible drawbacks of the normative classification of children into groups of competent and incompetent ones.

Overall, we should evaluate whether the clinical assessment of children's competence by an instrument is comprehensive, or that we miss out on important non-measurable factors. Finally, we need to consider if we are fully aware of the influence of developmental aspects affecting children's competence, and if this makes children's competence different from adults.'

In this article we will reflect on possible implications of the recent empirical findings on children's competence to consent considering normative, developmental, and clinical perspectives. Subsequently, we will derive recommendations for policies.

Discussion

Normative aspects

Considering children either competent or incompetent is a normative judgment. However, the fact that competence is a normative judgment does not mean that it cannot be informed by research data. Research shows that a competence assessment can be reliably performed using a structured tool like the MacCAT-CR. The MacCAT-CR's total and sub-scores showed a good reproducibility and the overall accuracy of MacCAT-CR scores in correctly classifying children as competent against the reference standard was high as well.(150) In addition, it was shown that using such a tool, three age groups could be distinguished: one in which children are most probably incompetent, one in which children are most probably competent, and a group in which probability of (in)competence is less clear (between 9.6 and 11.2 years). Such findings do not prescribe how ethics and law should deal with (in)competence and children. But, as we will discuss below, the findings may help to do justice to the capacities and challenges children may face when deciding about treatment and research options. For instance, for health care professionals, as well as parents, it is important to know that a structured and reliable tool for assessing competence in children is available. Performing such a structured competence assessment may clarify the capacities of an individual child in case professionals have doubt about the child's competence. In addition, the findings concerning the age groups may support the development of guidelines dealing with informed consent in children. Still, clearly, the ethical and legal norm for competence in children cannot be directly derived from these research findings. For instance, establishment of cutoff scores for competence is after all based on normative judgments.

Ethical Aspects

Rational Reasons versus Emotions and Values

Some authors have raised doubts about the validity of competence assessment by MacCAT-scales, and argued that the MacCAT-assessment puts the main emphasis on rational reasoning. Ethicists and other commentators bring into the discussion the role of values and emotions in competence. In the case of patients with anorexia nervosa, Hope and colleagues(164) suggest that to develop a better understanding of competence, research needs to be expanded by factors of competences not covered by the four criteria that are commonly applied (understanding, appreciation, reasoning, expressing a choice). Charland argues that MacCAT-scales seldom sufficiently recognize emotive components and values in decision-making competence.(165) He states that "pathological values" may be present in patients with anorexia nervosa or substance abuse disorders, which are both mental disorders that effect competence. He proposes to incorporate a measure of emotional competence into a competence assessment instrument before considering it a valid measure. Appelbaum, author of MacCAT-T, agrees that emotions aid humans in processing information but suggests that the feasibility of adding emotional capacity to the list of capacities essential for decisional competence should be demonstrated first.(166) No consensus in this debate has been reached yet. It is conceivable that in children "immature values" might be present that are not covered by competence assessment using MacCAT-scales. The study on accuracy of MacCAT-CR in children was performed using a reference standard established by experts. In cases of anorexia nervosa and substances abuse disorders the pathological values might be recognized by clinical experts, in children we might expect the clinical experts to have recognized immature values when present in children. If not, the study might have missed out on an unmeasured component of children's competence. This would then have resulted in considering more children competent using the MacCAT-CR than actually justified.

Legal Aspects

Age-Limits versus Case-by-Case Assessment

It is widely recognized that the evolving capacities of children and adolescents are reflected by a gradual development of decision-making competence.(133) The use of a fixed age-limit as cutoff for competence is defendable, since age is an efficient proxy for competence with considerable practical advantages as an administrative and normative gauge. It can be

measured easily and offers a clear framework. However, the disadvantage of fixed age-limits is the all or nothing character, meaning that relevant differences between individuals are not taken into account. With a set age-limit, some incompetent individuals above the limit will unjustly be deemed competent and some competent individuals below the limit unjustly deemed incompetent.

An alternative for the fixed age-limit is a case-by-case assessment of decision-making competence. A recent study has shown that doctors and researchers tend to judge a child to be competent if the child's decision conforms to their own ideas of the child's best interest.(5) This means that competence is gauged by the outcome of the decision rather than by the process of reasoning in deciding about participation. Data suggest that unstructured performance of competence assessments is often sub-optimal and hence the reliability of unstructured judgments has been poor.(2) To avoid this bias, a case-by-case assessment would require an objective assessment instead of the currently used intuitive one. The MacCAT-CR would be an appropriate instrument for this purpose in the research context and there are indications that MacCAT-T is feasible for use in the pediatric treatment setting.(134,150)

Reset Age-Limits

Age-limits for asking children's consent vary widely over nations and states.(133) In Europe, domestic law determines whether or not people are competent to consent to healthcare interventions.(11) In some countries autonomous decision-making is lawful only from 18 years onwards and in other countries minors are allowed to take healthcare decisions from a fixed age below legal majority, e.g., 12 years in the Netherlands and 15 years in Denmark(11) Another variant applied in most Canadian provinces and Switzerland is a flexible system stating that anyone who is capable can give informed consent, whereby competence is evaluated on a case-by-case basis.(11) In the United States, generally speaking, it often falls to parents or legal guardians to provide informed permission for medical decisions and children under 18 are to give assent.(126) Ideally, age-limits accomplish the goal of striking a proper balance in order to both protect children's interests when they are not fully able to do so themselves and to respect their autonomy when they can exercise it. So if a fixed age-limit is used, it must be generally in accordance with the developmental stages. Our research outcomes now offer scientific input for setting a reasonable and just age-limit; as far as we currently know the age-limit that presents closest accordance with children's competence is eleven or twelve years.

Children's Decision-Making Competence in Civil Law and Criminal Law
The development of decision-making capacities in children is not solely of importance in health law, but also considered in other juvenile laws e.g., civil law and criminal law. In many jurisdictions the age of twelve constitutes a cardinal point, for example regarding adjudicative competence. The age of twelve is not very different from the ages for competence resulting from the studies with MacCAT-CR and MacCAT-T. However, there are arguments mentioned in literature to reconsider these age-limits for juveniles' pre-adjudicative and adjudicative competence, and criminal responsibility, as adolescents in the criminal setting might show typical deficiencies in their decision-making due to additional risk-factors: for instance, lower intelligence, higher rates of psychiatric disorders and brain trauma's, higher prevalence of prenatal exposure to alcohol and drugs, exposure to violence and abuse, dysfunctional family backgrounds and substance abuse.(167) In addition, we should note that although there are certain similarities between competence and criminal responsibility, there are differences as well.(36)

Developmental Aspects

Difference between Competence Assessment in Adults and Children
In adults, patients are deemed competent unless the clinician has reasons to believe otherwise. In children, it is generally the other way around, they are presumed not to be competent in most jurisdictions.(126) Whereas in adults MacCAT-scales are merely used to ascertain incompetence in mentally compromised patients out of an overall competent population, in children it might be more important to discover competence in a mainly incompetent population. The application of MacCAT-scales in children puts higher demands on the specificity of the instrument; it serves to weed out the proportion of children that are correctly identified as competent from those (possibly incorrectly) identified as incompetent. In the MacCAT-CR study, specificity in children of 11.2 years and older was good: 90%.(150)

Parent versus Professional
Research showed that judgments of incompetence by parents frequently coincided with the MacCAT-CR incompetent classification, however parents' assessments of competence showed only moderate agreement with the MacCAT-CR standard. This might imply that parents express a higher expectation regarding their children's competence, assigning them more voice and responsibility, than professionals do. In literature the opposite

was described: in a sample of 120 young people undergoing orthopedic surgery in 1993, health professionals recommended a much lower mean age for competence than parents did (10.3 vs. 13.9).(137) The recent finding that parents judged their children more readily competent than clinicians, might be related to the specific dynamics of parent-child relationships.(14) Parents are expected to inhibit their child's impulsive, risky, and sometimes harmful behavior and to substitute the child's ineptitude and inability to judge situations, appropriate behavior and actions with their superior judgment. Parents tailor their parenting behavior to the specific abilities of the child. Children who are raised in a warm and understanding atmosphere are often able to present their part in a joint decision-making process at an early stage of their development.(16) An authoritative parenting style, which includes direction-giving and limit-setting, is positively related with an adolescent's capacity for autonomous decision-making.(20) In the medical context children might be capable of autonomous decision-making, albeit, within the guiding environment set by their parents. Possibly parents assign their children more decision-making competence than professionals do, because parents shape the family context and professionals regard the child more independently.

Assessment Must Cover Developmental Aspects

Differences between children and adults regarding decision-making competence have been found in the ability to restrain impulsivity and in the ability to place a given decision in a larger temporal context.(19) The inadequate capacity of children in risk assessment could be connected to the late full maturation of the frontal lobes that are essential for effective executive functions.(20) Adolescents generally do not fully possess the capacity to appreciate the long-term consequences of their choices until the age of 21.(20) Research demonstrated a difference between decision-making under low levels of arousal or in situations with low emotional upheaval (cold cognition), and thought processes under high levels of arousal and emotional valance (hot cognition).(167) Hot cognition may result in intuitive responses rather than carefully considered, rational responses.(167) Decisions on medical research participation involving information provision, rehearsal of information, time to consider, and reflection with parents, generally result in cold cognition decisions. Treatment decisions are more prone to hot cognition when involving time pressure or weighty risks. With the research results showing that children of 11.2 years and above have comparable decision-making capacities to adults concerning research participation, we need to consider their possible immaturity in decisions of a supervisory or

managerial nature normally made by their parents, for example overseeing the family agenda, or arranging transport to the hospital. Possibly, children are able to decide with cold cognition on research participation, but are less able to responsibly respond to, for example, unforeseen traffic situations and therefore need the dyadic relationship with parents who provide the necessary direction-giving and limit-setting.

Practical Aspects

From a practical point of view, assessment of all pediatric patients' competence on a case-by-case basis with an instrument would impose a heavy burden on patients, professionals, and the medical system. A selective implementation of a standardized competence assessment in exceptional cases would be preferable over a broad implementation (Table 8).

Table 8. Recommendations for Structured Assessment of Decision-Making Competence in Children in the Clinical Context

Context	Proposal	Comments
Treatment	– Individual cases: strike proper balance between protecting and respecting the child's interests – Children < 12 years: if competent in exceptional case with weighty decision – Children > 12 years: in case doubts exist on competence	– General population: burden on medical system, not much better than age limits
Research	– Individual cases: children between 10 and 12 years – Children > 12 years: in case doubts exist on competence – Feasible for research purposes at group level – Feasible in special research populations (intellectual disabled, psychiatrically ill)	– General population: burden on medical system, not much better than age limits

For the research context, under the age of 9.6 years children were generally incompetent to decide on research participation,(133) so an individual assessment does not seem profitable. Children between 9.6 and 11.2 years were in the change-over period, an individual assessment of competence might be applicable in this age group. Children of 11.2 years and above can generally be considered decision-making competent, no individual assessment is needed unless there are reasons to doubt a child's competence. In special

research populations like intellectual disabled children or pediatric patients with a psychiatric disorder that diminishes competence, a research protocol could include a standardized competence assessment of participants in order to warrant the interests of incompetent patients.

In the treatment context, there are no conclusive age-limits for competence established empirically, yet preliminary findings indicate agreements with the research context. An age-limit that is generally in accordance with the age that children reach decision-making competence could be applied; derived from the studies on MacCAT-CR and MacCAT-T a preliminary appropriate age may be 11 or 12 years. In case of doubt, competence will have to be assessed in children older than 12 years as well. Individual competence assessment of all pediatric patients in the change-over period might possibly overburden clinicians. However, it may be valuable to create the possibility for clinicians to take into account exceptional cases, such as the assessment of a child under the age of 12, seemingly competent, who has to make a weighty decision. In these cases an individual standardized competence assessment contributes to substantiate the exception.

Parents are generally provided with the legal authority to raise their children, assigning them rights and responsibilities. To achieve an equable consideration between the legal position of the child and that of the parents, a double consent procedure (child and parent) is recommended for minors from the age of 12 until majority. Even if we establish a child's decision-making competence regarding the medical decision at hand, a double consent procedure will do justice to developmental aspects of children and the specific characteristics of the parent-child dyad. The parental role is needed to offer extra protection by creating the context for the child's competent decision-making and by facilitating the child's long term autonomy.

Besides the advantages of a double consent procedure, there may be a disadvantage concerning possible disagreement between child and parent, which may require elaborated policies. In the Dutch situation experience has been gained with a double consent procedure and evaluation shows that disagreement between parent and child was not a concern.(168;169)

A double consent procedure is fundamentally different from a procedure of parental permission and child assent, and would imply a considerable shift regarding some current legislations. For instance, in the current Code for Federal regulations of the United States (13) by definition children are "persons who have not attained the legal age for consent to treatments or procedures involved in the research" (45CRF46.402(a)). The legal age of adulthood is a matter of local law, but is in a large majority of states 18 years.

Regulations state that some children might be able to give their assent, meaning an affirmative agreement. However, in research the institutional review board may still waive the assent requirement under certain circumstances (45CRF46.116). Some authors have proposed that children's assent should only be required from a fixed age of 14 years, based on theories of subject autonomy and child development.(170) The empirical evidence that children are generally competent not only to assent, but even to consent from the age of 12 offers a force opposing to these regulations and theories. There is no indication of a considerable difference in children's development between regions with widely varying policies regarding children's consent. These local variations in regulations may have evolved under the influence of historical, cultural, or emotional preferences, representing a local normative view. Empirical data now provide underpinnings for more evidence-based age limits in policies.

Limitations and Directions for Future Research

Although our recent empirical research provides substantial data to consider in debate and practice, many aspects of children's decision-making competence are still to be studied, of which we will name just a few. For instance, regarding medical decision-making, the age limits for reaching legal majority vary between countries and states from 16 to 21 years. Research does not show at what age a double consent procedure will no longer prove effective. In addition, more research is needed to demonstrate the validity of a cutoff score on a standardized assessment instrument for competence and the desirability of such a cutoff must be considered. In the treatment setting, more extended research on reliability and validity of the MacCAT-T in children is recommended. The importance of children's decision-making competence is not confined to the medical context alone but may be of significance to adjacent fields, for instance children's competence to proceed to criminal adjudication or to be consulted in civil procedures, which requires further research. Furthermore, new developments in neuropsychiatry may contribute to the understanding of the functioning of specific brain regions or connections that promote competent decision-making.

Summary

Research outcomes show that the legal concept of medical decision-making competence could be operationalized into a standardized assessment instrument for children in the clinical context. The MacCAT-CR proved

accurate for children's competence assessment in clinical research, preliminary findings show feasibility of MacCAT-T in the treatment setting. Developmental aspects, especially the fine-tuning of decision-making within the parent-child dyad, including the broader family context, are of importance in addition to a standardized competence assessment.

Policy recommendations include a selective implementation of individual assessment of children's competence in medical decision-making by a standardized tool in combination with practicable, generally appropriate age-limits. In the research context children can be deemed competent from the age of 12 and above, preliminary findings suggest the same age-limit for the treatment context. In the research context, case-by-case assessment of competence might be valuable in children in the change-over period between 10 and 12, in special research populations of mentally comprised patients, and in case of children older than 12 years when there are reasons to doubt their competence. In the treatment context, individual competence assessment might create an opportunity in exceptional cases to allow a competent child under the age of 12 to co-decide over significant medical interventions. A double consent procedure, including both child as well as parents, is recommended for children from the age of 12 until legal majority.

10 Summary and future perspectives in research on children's decision-making competence

Background

In this study, we have explored the issue of children's abilities to meaningfully decide on complex and important medical options, of which, until recently, little was known except that it often proved difficult to assess a child's competence in some clinical settings. Nor was there empirical evidence on children's competence to consent to treatment or clinical research to underpin these problematic areas. Yet problems did arise, when, for instance, pediatric patients did not agree with a recommended treatment. Or, when, in a research context, it remained unclear how to do justice to children's vulnerable population status while attempting to optimize their research participation.

As it stands, patients' competence to consent is usually assessed implicitly within the context of daily pediatric practice. However, lacking a gold standard, children's competence has continuously been assessed in an unstructured way, which has led to inconsistencies.(2) As we have shown, age standards prescribed by law may have had too much influence in clinicians' assessments. To complicate matters further, these legal age standards have varied widely between countries.(4) In addition, competence assessments were often influenced by the clinicians' idea of what was in the child's best interest.(5)

With our project we aimed at developing a standardized tool for assessing children's competence to consent and to offer empirical evidence to underpin age limits for alleged competence in children in order to optimize policies regarding children's decision-making in clinical situations.

Best Practices for Children's Competence Assessment

Having charted the latest developments in children's competence assessment in chapter 2, we concluded that little progress was achieved over the last decades. Partly, because the discussion on children's competence to consent to medical issues had been concentrated around complex normative concerns, a consensus over a clear operationalization of children's

decision-making competence was far from being reached (chapter 2). Consequently, little empirical research had been conducted on competence assessment in children. We suggested a possible empirical research agenda to make way for advancements. Moreover, we recommended that research data are needed to underpin theories and guidelines and advance regulations concerning children's decision-making competence in the medical context.

Assessment Instruments for Competence to Consent

As a starting point, the accuracy of existing tools for assessing competence to consent used in clinical populations were examined (chapter 3). Although many different instruments were described, few were tested in a systematic way. We concluded that studies on the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)(3) show clear indications of reliability and validity in adult populations.(150) Used alongside the MacArthur Competence Assessment Tool for Treatment (MacCAT-T), the MacCAT-CR often proved to be the best assessment tool available.

A study protocol on how to assess children's competence to consent to clinical research was developed in chapter 4. The MacCAT-CR was translated and adjusted for use in children aged 6 to 18,(4) which included the use of simple language to be understood by elementary school-aged children, and additional questions on the influence of relationships with parents and peers. Research was implemented by using a sample of 161 pediatric patients visiting inpatient and outpatient clinics of pediatric departments of allergology, gastroenterology, oncology, ophthalmology and pulmonology. Clinical research projects on offer included 3 observational studies and 10 randomized clinical trials.

Results of this study (chapter 5) showed that children's competence to consent to clinical research can be assessed validly and reliably using the MacCAT-CR.(150) In the same study, the 4 domains representing competence in most jurisdictions (understanding, appreciation, reasoning, and expressing a choice) appeared to constitute a single trait or continuum of competence in children. Hence, a cutoff score on the MacCAT-CR above which competence was likely could be estimated.

Age Limits for Competence to Consent in Children

Our research showed that age limits for children to be deemed competent to decide on research participation could be estimated as follows: children

of 11.2 years and above generally appeared to be competent, whereas children of 9.6 years and younger were generally not competent (chapter 5). A change-over occurred between 9.6 and 11.2 years, and the cross-over point was estimated at 10.4 years.(150)

For treatment decisions, a preliminary study using MacCAT-T on decisions about predictive genetic testing, revealed that most children above the age of 11.8 were competent to consent (chapter 7). The results from these studies in the research and in the treatment context show that MacCAT-scales modified for children are practicable in both settings and offer a preliminary indication that age-limits for competence do align.

Factors Affecting Children's Competence to Consent

Out of all the factors that were considered to influence children's competency, the key determining factor was age (chapter 6). Intelligence, on the other hand, was of little influence, its contribution to competence was small and inconsequential. The theory-based assumptions that risk and complexity of the decision would be related to a competence classification could not be confirmed with empirical data,(130) meaning that for radical decisions that imply a higher level of competence a more mature age is not necessarily required. This may indicate that children of a certain age who are able to make less complex/low risk decisions could possibly also make high complex/high risk decisions at that same age. A possible explanation for this may be that children at a certain age possess the required capacities, and that competent decision-making is then possible when the information they receive is of good quality. For the other potential determining factors for competence shown by previous studies, like gender, the influences of social relationships, disease experience, ethnicity, and socio-economic status, no clear relationship with competence could be demonstrated either. Interestingly, parents judged their child more readily competent than experts did.(130)

Considering Implications of Empirical Knowledge for Policymaking

Ethics, law, and clinical practice can benefit from these research data, even though assessment of children's competence has a normative character (chapter 9). The research results may help validate the capacities of children when they face treatment and research decisions.(171) Since age is an efficient proxy for competence, it is conceivable to use a fixed age-limit as cutoff for competence. Our research outcomes thus offer scientific input

for setting a reasonable and just age-limit; as far as we currently know the age-limit that presents closest accordance with children's competence is 11 or 12 years. However, fixed age-limits bear the disadvantage of an all or nothing character, meaning that relevant differences between individuals are not taken into account. If a more precise case-by-case assessment of children's competence is required, the MacCAT-CR would be an appropriate instrument for this purpose in the research context.(171)

Assessment of all pediatric patients' competence on a case-by-case basis with an instrument would impose a heavy burden on patients, professionals, and the medical system, and will therefore be untenable and unsuitable. Although, dismissing a case-by-case assessment out of hand is inadvisable. A selective implementation of a standardized competence assessment in exceptional cases would be preferable.(171) Considering the research context, children were generally found competent from the age of 12 years and above, and incompetent under the age of 10, thus individual assessment in these age groups would be undesirable. For a case-by-case assessment of competence to have considerable value, the children in the change-over period between 10 and 12 years, whose competence is unresolved, should be focused on. Likewise, in special research populations of mentally compromised patients, and in case of children older than 12 years when there are reasons to doubt their competence, a case-by-case competence assessment can be recommended. Preliminary findings indicate similar age-limits for the treatment context; however, further research is needed to confirm those results. In the treatment context, individual competence assessment might create an opportunity in exceptional cases to allow a competent child under the age of twelve to co-decide over significant medical interventions.

In any case, where children are concerned we also need to take into account the developmental aspects. On the one hand, we have the research results showing that children of 11.2 and above have comparable decision-making capacities to adults concerning research participation, but on the other we need to consider their possible immaturity in decisions of a managerial or supervisory nature. It might be possible that children are able to decide with careful deliberation to participate in research, but are less able to responsibly respond to, for example, unforeseen traffic situations or coinciding agendas of other family members. Children, even competent ones, may still need the dyadic relationship they have with their parents, who give them the direction they need and who set limits that provide them with the necessary structure and security that, in turn, could help facilitate the decision-making process.(171)

In addition, the research results must especially be interpreted against a background where parents are generally provided with the legal authority to raise their children; that is, by law they have rights and responsibilities to ensure the well-being of their child. To achieve an equable consideration between the legal position of the child and that of the parents, a double consent procedure (child and parent) is recommended for minors from the age of 12 until majority. Even if we were to establish a child's decision-making competence regarding a clinical decision, a double consent procedure would take into consideration the potential developmental aspects of children, the specific characteristics of the parent-child dyad, and the position of the parents.(171)

Non-participation of Children in Research

As we revealed, there is a dire need for more pediatric drug trials since currently an alarming percentage of drugs (36-90%) prescribed to children are not being tested in their age group.(125) Whereas specific pediatric regulations warrant children's safety, their recruitment for these trials remains one of the main difficulties. For this reason we investigated potential determining factors of children's non-participation in clinical research, in order to optimize their research participation by recommending improved recruitment strategies (chapter 8). We performed a qualitative and quantitative analysis of reasons why participation rates of children in clinical research are problematic.

In our sample of 161 pediatric patients eligible for clinical research participation, we ascertained that 60% did not participate (39% decided not to participate, 21% was indecisive).(133) Factors that predicted non-participation were lower age, less disease experience, and less complex research with lower risk. Decisive reasons for non-participation expressed by children were time constraints and extra burdens brought about by the research procedures. We discussed that strategies to optimize research participation should be aimed at younger children and their families, who are logistically challenged, and unfamiliar with health care and research. Recommendations for optimizing children's research participation, we argued, would involve informing pediatric patients and their families of the value of research; coaching of children and parents in order to minimize logistic burdens; and improving accessibility.(133)

Future Perspectives

Although our present empirical research provides substantial data to consider in debate and practice,(171) many aspects of children's decision-making

competence are still to be studied. We will consider some possible areas of future research, concerning the medical context as well as the forensic context.

Children's Competence to Consent to Treatment

In the treatment setting, more extended research on reliability and validity of the MacCAT-T in children is needed. There are several pediatric and psychiatric settings where children's competence can be an issue of importance. One of those settings might be the specialized gender dysphoria clinic for children, where competency issues play a significant role.

The rise in awareness about gender dysphoria (GD) in youth we are currently experiencing in the media and general population is leading to an increase in referrals to specialized clinics, not only in the Netherlands but also in the rest of Europe and the United States. Leading evidence suggests that puberty suppression that relieves the acute distress of physical puberty typical for GD seems to offer these youths the possibility of a healthy psychological development.(172;173) Medical interventions that occur after puberty may be accompanied by irreversible physical changes and less favorable psychological outcomes. This implies that a complex medical treatment decision needs to be made by families and children around the age of 12 or younger, especially in natal females, with a mean age of 11 years at the start of puberty. Although puberty suppression implies, in principle, a reversible intervention, the start of treatment with cross-sex hormones (CSH) includes irreversible changes and consequences for fertility. Taking into consideration the possible side-effects of a prolonged puberty blocking of more than 3 years, like for instance lowered bone density (Klink et al, unpublished data), decisions to intervene with cross-sex hormones should be made at an earlier age than 16 years. Both intervention and nonintervention may carry risks to the welfare of the child.(174)

We have shown that local jurisdictions, which determine the age limits for children's alleged competence, vary widely between countries.(26) In the Dutch situation, two age limits apply: 12 years for deeming a child competent to consent to treatment together with parental consent, and 16 years for deeming a child competent to give independent consent. To date, these fixed age limits have been a leading principle in medical interventions for GD. However, they do not seem to be applicable in case of medical intervention with puberty blockers or CSH, because puberty often starts before the age of 12, and consequently, CSH should be started before 16 years.(175)

Because no methods are yet available to establish medical decision-making competence in children, such competence is judged in intuitive

rather than standardised ways, leaving many developmental, ethical, and legal issues uncertain. Future research is needed on developing an instrument that assesses children's competence to consent to medical treatment. By extension, it is vital that research on the extent of children's competence to consent to medical interventions and on empirical evidence for estimating age limits for children's alleged competence is being realized.

Forensic Psychiatry and Children's Decision-Making Competence

The importance of children's decision-making competence is not confined to the medical context alone but may be of significance to adjacent fields as well: it could benefit, for instance, the competency assessment in criminal adjudication or civil procedures, which requires further research.

Recently, interesting similarities between assessments of criminal responsibility and assessments of competent decision-making within the context of informed consent were observed, whereby some authors conceived the assessment of criminal responsibility in terms of a decision-making process.(176) In both contexts, autonomy and decision-making would be central factors. Accepting this basic similarity would indicate that research on criminal responsibility could be directly informed by research on competent decision-making.(177) Although there are certain similarities between competence and criminal responsibility, we must realize that there are considerable differences as well.(36)

In child and adolescent forensic psychiatry, a broad assessment of the child's capacities is conducted in order to advise the court on his/her accountability in unlawful acts. This is done because adolescents in the criminal setting might be exposed to typical factors that influence decision-making: lower intelligence, higher rates of psychiatric disorders and brain trauma's, higher prevalence of prenatal exposure to alcohol and drugs, exposure to violence and abuse, dysfunctional family backgrounds, and substance abuse.(167)

Internationally, determining the age-limits for deeming a minor able to stand trial differ between jurisdictions. Some countries might require an assessment of adjudicative competence to deem the defendant capable to stand trial, others might only assess criminal responsibility, while others still might apply both. Nonetheless, these assessments are to take into account the maturity of the minor's decision-making capacities as well as possible psychopathology. In adults, decision-making competence and criminal responsibility are, although related, still considered to be two separate concepts.(36) Future research may elicit if and how decision-making competence and criminal responsibility intertwine in minors and if the

concepts should be regarded separately or concomitantly. Considerable differences between legal systems regarding the criteria for legal insanity will have to be considered carefully. Since some juvenile justice systems seem to move from a rehabilitative model to a more punitive model, it is vital to satisfactorily resolve questions on juvenile's decision-making competence and criminal responsibility.

Neuroscience and Children's Decision-Making Competence

Furthermore, new developments in neuropsychiatry may contribute to the understanding of the functioning of specific brain regions or connections that promote competent decision-making. For instance, currently, extensive neuroscience research is being done on the impact of mental disorders on specific components of decision-making; for example, decision-making deficits in addiction and in impulse-control disorders.(178) Neurolaw is an example of such a developing interdisciplinary area of research that investigates the significance of the neurosciences in relation to the law from different perspectives.(179) Now that the role of neuroscience for adult law is increasingly being studied, the perspectives that neuroscience could offer for juvenile law also come into sight. Research is needed to examine the possibilities – and pitfalls – of using neuroscientific methods (e.g. fMRI or spect) to inform the judge in juvenile court cases on the development of brain areas relevant for decision-making.

Conclusion

Empirical research on children's competence to consent has yielded significant knowledge to be considered for policymaking. The present studies showed that children's competence to consent to clinical research can be assessed validly and reliably using the MacCAT-CR, and feasibility of the MacCAT-T for assessing children's competence to consent to treatment was confirmed. Using the MacCAT-CR, age limits for children to be deemed competent to decide on research participation could be estimated: children of 11.2 years and above generally appeared to be competent, whereas children of 9.6 years and younger were generally not competent. The key determining factor, out of all the factors that were considered to influence children's competency, was age. Considering the implications of these empirical findings for law, ethics and clinical practice, we recommended that 12 years would be a just age-limit for asking children's consent to clinical research. We argued that a double consent procedure, including both parent and child, would seem advisable for minors from the age of 12 until

majority, taking into consideration the potential developmental aspects of children, the specific characteristics of the parent-child dyad, and the position of the parents. Furthermore, in special research populations or when there are reasons to doubt a child's competence, case-by-case assessment is now possible in a standardized manner. In order to optimize children's research participation, we suggested improved recruitment strategies, which would involve informing pediatric patients and their families of the value of research, and coaching of children and parents in order to minimize logistic burdens.

Still, many aspects of children's decision-making competence are to be studied. For instance, in the treatment setting, more extended research on reliability and validity of the MacCAT-T in children is needed, especially in some pediatric and psychiatric settings where children's competence can be an issue of importance. One of those settings might be the specialized gender dysphoria clinic for children, where it is vital that research on the extent of children's competence to consent to medical interventions is being realized, even as on empirical evidence for age limits for children's alleged competence. Furthermore the similarities and differences between decision-making competence and criminal responsibility should be studied, and the possible opportunities offered by the developing field of neuroscience for assessment of decision-making competence should be explored.

Nederlandse Samenvatting

Inleiding

Kinderen nemen slechts in beperkte mate deel aan medisch wetenschappelijk onderzoek in vergelijking tot volwassenen. Een rol daarbij speelt dat zij worden gezien als onvoldoende wilsbekwaam en te kwetsbaar om blootgesteld te worden aan de extra belasting en risico's die meedoen aan onderzoek met zich meebrengt. Het ongewenste gevolg hiervan is dat belangrijke informatie over de werking van medicatie bij kinderen in veel mindere mate beschikbaar is dan bij volwassenen. Paradoxaal genoeg doet zich nu de situatie voor dat zieke kinderen in de praktijk medicijnen krijgen die minder goed bij hen zijn onderzocht, waardoor ook juist extra risico's optreden. De mate waarin kinderen wilsbekwaam zijn om zelf te beslissen over het meedoen aan medicatieonderzoek is nooit goed onderzocht.

In de dagelijkse kindergeneeskundige praktijk wordt wilsbekwaamheid bij kinderen meestal impliciet beoordeeld, omdat clinici niet weten welke standaard ze moeten gebruiken.(2) De betrouwbaarheid van deze impliciete beoordelingen is laag. En doordat er geen standaard is, zijn de wettelijk vastgelegde leeftijdsgrenzen voor wilsbekwaamheid meestal richtinggevend. Deze leeftijdsgrenzen verschillen echter behoorlijk tussen landen.(4) Een ander probleem is dat clinici er toe neigen om een kind wilsbekwaam te beoordelen, als de keuze van een kind overeenkomt met dat wat een clinicus zelf het beste vindt. (5)

Dit waren redenen om onderzoek te doen naar wilsbekwaamheid bij kinderen in de klinische praktijk, met als doel het ontwikkelen van een gestandaardiseerde methode voor beoordeling van wilsbekwaamheid bij kinderen en het vaststellen van passende leeftijdgrenzen om kinderen wilsbekwaam te achten ten aanzien van medische beslissingen.

Stand van zaken

We zijn begonnen met het in kaart brengen van recente ontwikkelingen in het beoordelen van wilsbekwaamheid in de kindergeneeskundige praktijk. De afgelopen decennia is een brede discussie gevoerd over belangrijke normatieve aspecten van wilsbekwaamheid bij kinderen, maar voor de klinische praktijk heeft dit nog niet tot veel veranderingen geleid (hoofdstuk 2). In de hoofdzakelijk theoretische discussie bleek het moeilijk om

tot consensus te komen, en hierdoor was het ook lastig om een operationalisatie van het begrip wilsbekaamheid voor de klinische praktijk te ontwikkelen. Onderzoek naar wilsbekwaamheid bij kinderen in de praktijk is dan ook zeer beperkt. We deden een voostel voor een onderzoeksagenda, met als hoofddoel het verzamelen van meer empirische gegevens over wilsbekwaamheid bij kinderen. Gegevens uit empirisch onderzoek zijn nodig om theorieën en richtlijnen te kunnen onderbouwen, om daarmee recht te doen aan de positie van kinderen aangaande medische beslissingen.

Meetinstrumenten

De bestaande instrumenten voor het bepalen van wilsbekwaamheid zijn onderzocht in een overzichtsartikel (hoofdstuk 3). Hoewel er veel instrumenten ontwikkeld zijn, is er weinig onderzoek gedaan naar de betrouwbaarheid en validiteit van deze instrumenten. Na analyse van onderzoeksgegevens van de bestaande instrumenten is de conclusie, dat de MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) (3) het best is onderzocht en dat betrouwbaarheid en validiteit is aangetoond in de volwassen populatie.(150) Daarnaast is de MacArthur Competence Assessment Tool for Treatment (MacCAT-T) het meest veelbelovend voor de behandelsetting, hoewel de validiteit en betrouwbaarheid nog niet zijn aangetoond.

We presenteren de opzet van ons onderzoek naar beoordeling van wilsbekwaamheid bij kinderen ten aanzien van medisch wetenschappelijk onderzoek in hoofdstuk 4. Voor dit onderzoek werd de MacCAT-CR in het Nederlands vertaald en aangepast voor gebruik bij kinderen van 6 tot 18 jaar.(4) Deze aanpassingen betroffen eenvoudig en kindvriendelijk taalgebruik en toegevoegde vragen over de invloed van ouders en vriend(inn)en op de beslissing.

Het onderzoek werd uitgevoerd op verschillende kindergeneeskundige afdelingen (allergologie, gastro-enterologie, oncologie, oogheelkunde, pulmonologie) en in totaal deden 161 kinderen mee (hoofdstuk 5). De deelnemende kinderen waren patiënten die in werkelijkheid voor de keuze stonden om mee te doen aan lopende onderzoeksprojecten in de kindergeneeskunde, waaronder in 3 observationele studies en 10 gerandomiseerde klinische studies.

De resultaten van dit onderzoek (hoofdstuk 5) lieten zien dat wilsbekwaamheid bij kinderen op een betrouwbare en valide manier kon worden vastgesteld met de MacCAT-CR.(150) Ook liet het onderzoek zien dat de 4 domeinen van wilsbekwaamheid (begrip, redeneren, op waarde schatten en een keuze uiten), die bij volwassenen als afzonderlijke onderdelen worden onderscheiden, bij kinderen één continue schaal uitmaken. Hierdoor was

het mogelijk een afkappunt op de MacCAT-CR te berekenen waarboven wilsbekwaamheid waarschijnlijk was.

Leeftijdsgrenzen

De volgende leeftijdsgrenzen werden gevonden voor wilsbekwaamheid bij kinderen ten aanzien van onderzoeksdeelname (hoofdstuk 5): kinderen onder 9.6 jaar waren over het algemeen niet wilsbekwaam, kinderen boven de 11.2 jaar wel, en daar tussen in was een overgangsgebied.(150)

Voorlopige resultaten van een onderzoek met de MacCAT-T in een populatie kinderen die moesten beslissen over voorspellend genetisch onderzoek, gaven aanwijzingen dat in de behandelcontext de meeste kinderen wilsbekwaam waren vanaf de leeftijd van 11.8 jaar (hoofdstuk 7). De MacCAT-T is evenals de MacCAT-CR goed toepasbaar bij kinderen en er is een voorlopige indicatie dat de leeftijdsgrenzen voor wilsbekwaamheid ten aanzien van onderzoeksdeelname en van medische behandelbeslissingen niet ver uit elkaar liggen.

Beïnvloedende Factoren

De belangrijkste voorspellende factor voor wilsbekwaamheid was de leeftijd van het kind, met daarnaast een kleine invloed van de intelligentie (hoofdstuk 6). In de literatuur is beschreven dat de mate van wilsbekwaamheid gerelateerd moet worden aan de complexiteit en het risico van de beslissing, echter uit de uitkomsten bleek dat ingewikkelder of risicovoller beslissingen op dezelfde leeftijd konden worden genomen als eenvoudiger en minder risicovolle beslissingen.(130)

Ook voor andere factoren die uit de literatuur naar voren kwamen als mogelijk beïnvloedend voor wilsbekwaamheid, zoals geslacht, de invloed van sociale relaties, ervaring met ziekte, etniciteit, en sociaaleconomische klasse, werd geen voorspellende waarde voor de wilsbekwaamheid gevonden. Opvallend was wel, dat ouders hun kind eerder wilsbekwaam inschatten dan clinici.(130)

Implicaties voor Beleid

Het vaststellen van wilsbekwaamheid bij kinderen heeft een normatief karakter, maar desalniettemin kunnen de onderzoeksuitkomsten van waarde zijn voor het medisch-ethisch en juridisch debat en de kindergeneeskundige

praktijk (hoofdstuk 9). De uitkomsten van het empirisch onderzoek kunnen er juist toe bijdragen dat er meer recht wordt gedaan aan de vaardigheden van kinderen die medische beslissingen moeten nemen maar ook aan de moeilijkheden die ze er mee hebben.(171)

Het hanteren van een vastgestelde leeftijdsgrens voor wilsbekwaamheid bij kinderen heeft zowel voor- als nadelen. Leeftijd is een efficiënte en praktisch goed toepasbare maat. Echter, door het gebruik van een vaste leeftijdsgrens zullen relevante individuele verschillen in wilsbekwaamheid tussen kinderen niet tot hun recht komen. De onderzoeksuitkomsten maken het nu mogelijk om een leeftijdsgrens vast te stellen die wetenschappelijk is onderbouwd, en die ligt bij 11 of 12 jaar. Tegelijkertijd is het nu mogelijk om in situaties die vragen om een nauwkeuriger beoordeling van wilsbekwaamheid in de onderzoekscontext, dit individueel te bepalen door gebruik te maken van de MacCAT-CR.(171)

Praktisch gezien zou het een enorme belasting zijn voor kinderen, ouders en clinici als de wilsbekwaamheid bij elke pediatrische patiënt individueel zou moeten worden vastgesteld met behulp van een instrument. Daarom is een selectieve implementatie van het instrument voor uitzonderingssituaties te verkiezen boven een brede implementatie.(171) In de onderzoekscontext kunnen kinderen van 12 jaar en ouder over het algemeen wilsbekwaam worden geacht. Een individuele beoordeling van wilsbekwaamheid kan meerwaarde hebben bij de groep kinderen in de overgangszone tussen 10 en 12 jaar. Ook in speciale onderzoekspopulaties zoals bijvoorbeeld kinderen met een verstandelijke beperking, of bij kinderen ouder dan 12 jaar waarbij er redenen zijn om aan hun wilsbekwaamheid te twijfelen, kan beoordeling met de MacCAT-CR worden ingezet. Voorlopige bevindingen geven aanwijzingen voor een vergelijkbare leeftijdsgrens voor wilsbekwaamheid in de behandelcontext. Hier zou een individuele beoordeling van wilsbekwaamheid bij kinderen onder de 12 jaar bij uitzondering ingezet kunnen worden, wanneer een kind goed in staat lijkt om mee te beslissen in geval het over zwaarwegende medische interventies gaat.

Bij kinderen is een belangrijk feit dat ze in ontwikkeling zijn. Er is nu wel vastgesteld dat kinderen over het algemeen vanaf 11.2 jaar, overeenkomstig volwassenen, goed in staat zijn om te beslissen over deelname aan medisch wetenschappelijk onderzoek, maar we weten niet of ze ook aanpalende beslissingen wilsbekwaam kunnen nemen. Mogelijk dat kinderen op een weloverwogen manier kunnen beslissen over onderzoeksdeelname, maar nog minder wilsbekwaam zijn ten aanzien van beslissingen in onvoorziene complexe verkeerssituaties, of over de planning van de gezinsagenda, of het organiseren van vervoer naar het ziekenhuis. De relatie tussen kinderen

en ouders blijft daarom nog van groot belang zolang de ouders grenzen aangeven en bijsturing geven rondom beslissingen van het kind.(171) Bovendien ligt het wettelijk gezag over de opvoeding van het kind normaal gesproken bij de ouders, waardoor de ouders belast zijn met rechten en verantwoordelijkheden. Om tot een evenredige afweging tussen de positie van het kind en die van de ouders te komen, lijkt een dubbele consent procedure (van ouder en kind) het meest aangewezen voor kinderen vanaf 12 jaar tot meerderjarigheid. Zo'n dubbele consent procedure doet ook recht aan de ontwikkelingsaspecten van kinderen en aan de specifieke kenmerken van de ouder-kind dyade.(171)

Deelname van Kinderen aan Onderzoek

Er is meer onderzoek nodig naar effecten van medicatie bij kinderen, maar ondanks regelingen die de veiligheid waarborgen, is het rekruteren van voldoende kinderen die mee doen een groot probleem. We hebben onderzocht wat redenen zijn waarom kinderen niet deelnemen aan onderzoek, door een kwantitatieve en een kwalitatieve analyse te doen van factoren die mogelijk onderzoeksdeelname bemoeilijken (hoofdstuk 8).

In onze populatie van 161 kinderen deed 60% niet mee aan de voorgestelde onderzoeksprojecten (39% besloot om niet mee te doen en 21% nam geen beslissing).(133) Kinderen die jonger waren, die minder ervaring hadden met ziekte, en die moesten beslissen over eenvoudiger en minder risicovol onderzoek, waren minder geneigd om deel te nemen. Kinderen noemden zelf als belangrijkste redenen om niet mee te doen dat ze te weinig tijd hadden en dat ze de onderzoeksprocedures belastend vonden. Strategieën om onderzoeksdeelname door kinderen te verbeteren zouden gericht moeten worden op de groep jonge kinderen en hun ouders, op hen die niet goed bekend zijn met de gezondheidszorg, en op kinderen en ouders die moeite hebben met de logistieke aspecten van deelname. Aanbevolen wordt om kinderen en ouders beter te informeren over het nut van medisch wetenschappelijk onderzoek voor de behandelpraktijk, om de logistieke belasting zo veel mogelijk te verminderen, en om onderzoek toegankelijker te maken.(133)

Toekomstperspectieven

Met de uitkomsten van het empirisch onderzoek hopen we een voortzetting van het debat over wilsbekwaamheid bij kinderen te voeden en

onderbouwing te geven aan beleidsmakers ten aanzien van toekomstige regelgeving.(171) Er blijven natuurlijk nog vele aspecten betreffende wilsbekwaamheid en beslisvaardigheden bij kinderen over voor toekomstig onderzoek. Verder onderzoek naar wilsbekwaamheid bij kinderen in de behandelsetting is nodig, waarbij ook de validiteit en betrouwbaarheid van de MacCAT-T onderzocht moet worden. Verder kan de relatie tussen het concept wilsbekwaamheid of beslisvaardigheden in de medische setting, en het concept toerekeningsvatbaarheid in de forensisch-psychiatrische setting, nader in kaart worden gebracht. En tot slot verdient het aanbeveling om de mogelijkheden van neurowetenschappelijk onderzoek naar wilsbekwaamheid en beslisvaardigheden bij kinderen te exploreren.

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Dankwoord

Zonder hulp en inzet van vele anderen zou dit proefschrift niet tot stand gekomen zijn. Bij deze wil ik iedereen bedanken die hieraan heeft bijgedragen. Graag wil ik in de eerste plaats de patiënten en ouders die hebben geparticipeerd aan het onderzoek bedanken, ik ben onder de indruk van hun moed. Daarnaast dank ik de teams in de ziekenhuizen die hebben meegedaan aan de uitvoering voor hun grote inzet en deskundigheid. Een aantal mensen wil ik in het bijzonder bedanken voor hun betrokkenheid.

Hoe het begon

In 2008, tijdens mijn eerste stage voor de specialisatie kinder- en jeugdpsychiatrie bij de Bascule, begon ik met het schrijven van wetenschappelijke artikelen. Chaim Huyser, bedankt dat jij me op het spoor hebt gezet, mijn eerste artikelen schreef ik met jou. Het idee voor een groter onderzoek begon te groeien in 2009, waarbij Anne-Pauline Cohen en Frits Boer me op het idee brachten van kwesties rond wilsbekwaamheidsbeoordeling bij kinderen.
Pieter Troost, jij hebt een cruciale rol gespeeld in de aanvang van mijn promotieonderzoek, door me met woord en daad bij te staan in de uitwerking van een idee tot een ZonMW subsidieaanvraag. Wat ben ik blij dat je ook daarna, ondanks dat je ook binnen de organisatie nieuwe functies op je nam, altijd betrokken bent gebleven en met vele goede suggesties, zowel praktisch als filosoferend, hebt bijgedragen aan dit project. Ramón Lindauer die ook mee heeft geschreven aan de aanvraag, zorgde voor de academische inbedding in zijn inspirerende onderzoeksgroep en hielp op alle momenten bij het tackelen van formele procedures. Ook alle anderen die hebben meegeschreven aan de aanvraag wil ik van harte bedanken: Martine de Vries, Michel Zwaan, Elizabeth Vroom, Martin Offringa, Robert Lindeboom en Alice Broersma.

Promotoren en copromotoren

Hans van Goudoever, dank voor de efficiëntie waarmee we te werk zijn gegaan, met je ervaring, overzicht en support heb je veel bijgedragen aan de totstandkoming van de publicaties.

Ramón Lindauer, vier jaar lang ben je opgetreden als mijn onofficiële promotor, en in die tijd heb je me vertrouwen en ruimte gegeven om mijn eigen weg te vinden als onderzoeker. Ondanks de roerige tijden bleef je koers houden en ik hoop dat jij net zo veel plezier hebt gehad aan dit promotietraject als ik.
Pieter, je was de drijvende (copro)motor van het project, onvervangbaar, mijn dank is groot!

Leescommissie

Graag wil ik Prof. dr. Pieter Hoekstra, Prof. dr. Johan Legemaate, Prof. dr. Thomas Grisso, Prof. dr. Dick Willems, Prof. dr. Arne Popma en Mw. Prof. Dr. Martha Grootenhuis bedanken voor de kritische beoordeling van mijn proefschrift.

Het MacKID-team

Ik bedank alle betrokkenen (kinderartsen, arts-assistenten, research verpleegkundigen) die hebben bijgedragen aan het uitvoeren van de MacKID-studie in Amsterdam (AMC en VUmc), Rotterdam (Erasmus MC en Havenziekenhuis) en Den Haag (Medisch Centrum Haaglanden).
Speciaal wil ik hierbij noemen:
Jeroen van Setten, dank voor het opzetten van de internetapplicatie en beantwoorden van alle vragen die er uit volgden.
Joost Daams, als search-expert onmisbaar bij elke review!
Marc Benninga, bedankt voor de enthousiaste inzet en grote praktische bijdrage.
Michel Zwaan, altijd even druk en tóch op de juiste momenten daar.
Martine de Vries, veel dank voor je bijdragen vanuit medisch-ethisch perspectief.
Elizabeth Vroom, dank voor de ondersteuning en menselijke maat.
Dannis van Vuurden en Suzanne Gordijn, druk en betrokken, jullie hebben ons weer een stuk verder geholpen met jullie bijdrage.
Inekee van der Vaart en Marian Cavazza, onmisbaar waren jullie met jullie schat aan praktijkervaring.
Robert Lindeboom, wat een wijsheid en een statistisch kunstenaarschap!
Ellen van Minderhout, mede door jouw open houding en onderzoeksgeest is het gelukt dit project tot een goed einde te brengen.

Imke Christiaans, met je rustige inzicht wist je het beste van de samenwerking te maken.
Alice Broersma, fijn dat je altijd met advies over de ingewikkelde juridische zaken klaarstond.
Viola ten Hoorn, dank voor de vakkundige ondersteuning in de Engelse taal.
En mede-auteurs: Gerben Meynen, je vergezichten bieden een stip op de horizon.
Catherijne Knibbe, dank voor je bijdrage vanuit je uitgebreide ervaring.

Collega's AMC afdeling Kinder- en Jeugdpsychiatrie, de Bascule

In de onderzoeksjaren heb ik veel geleerd op het gebied van wetenschap mede dankzij mijn collega's van de onderzoeksafdeling Kinder- en Jeugdpsychiatrie van het AMC. Else, Julia, Lidewij, Els, Maj, Caroline, Mariëlle, Eva, Marthe, Inger, Vivian, Marieke, Carola, Rosanne, Judith, Jasper, Esther, hartelijk dank voor deze leuke jaren. Veel succes met jullie verdere (zeer diverse) carrières. Secretaresses Suzan Jansen en Susan Mosk, jullie waren en zijn de spil van de afdeling. Hartelijk dank voor alle ondersteuning en jullie luisterend oor. Onderzoeksassistenten Marjolein en Lotte: jullie waren onvervangbaar, jullie hebben elk je eigen kwaliteiten die onmisbaar waren voor het onderzoek en daarnaast was het fijn om met jullie te werken.

Afdeling Kind en Gezin van Stichting Centrum 45

Natuurlijk wil ik ook alle collega's van Centrum 45 heel hartelijk bedanken dat jullie me hebben gesteund in het aanhouden van mijn twee banen, waardoor de tijd altijd moest worden verdeeld. Bestuur Jan Schaart en Jan-Wilke Reerds, directeuren Ruud Jongedijk, Twan Driessen en Pim Scholten, al mijn directe collega's in Diemen met in het bijzonder Geert, Adriana, Jacolien, Julia, Jelly, Harry, Gerdie, Rembrant, Karen en Paulina, en de Oegstgeestse club Annemarie, Hans, Helen, Patricia, Aram, Trudy, Marloes, Anja, Karin, sociotherapeuten, en iedereen die ik gezien de ruimte niet kan noemen: dank voor jullie interesse. Ik ben erg blij om met jullie samen te werken.

Paranimfen

Saskia en Judith, mijn paranimfen, ik vind het heel bijzonder om jullie aan mijn zijde te hebben tijdens de promotie.

Familie en vrienden: mijn basis

Als eerste bedank ik mijn ouders, voor jullie steun door de jaren heen: An, en On die er niet meer bij is, maar altijd voorspeld heeft dat ik geschikt was voor de wetenschap. Mijn lieve zus Saskia en haar gezin: Matthijs, Robert en Judith. Niek en Mechteld, Heleen en Frank, Klaartje en Tiago, Daan en Fréderique, en jullie kinderen: jullie zijn er altijd bij belangrijke momenten, dank voor jullie steun en interesse.

Al mijn vrienden wil ik bedanken voor de belangstelling, steun en gezelligheid na(ast) het werk. Gina, Ruth, Marleen, Hester, Anja, Irma, Esther, Jessica, Wytske, Peter, Tjarda, Jim: de laatste jaren hebben we regelmatig over dit proefschrift en over jullie werk gesproken maar de gesprekken gingen ook over andere belangrijke en leuke zaken van het leven.

Mijn intervisieclubje wil ik bedanken voor de support en inzichten.

Lieve Lobo- en Sloterpoortburen, wat een geluk om naast jullie te wonen!

Zonder Milena en Hanneke zou ons gezin niet kunnen functioneren, dank voor jullie flexibiliteit en zorg voor onze kinderen.

Gijs, Boris, Oscar, Kasper

Lieve Boris, Oscar en Kasper, ik vind jullie geweldig. Door jullie besef ik keer op keer dat het zoeken van een verloren stuiterbal onder de bank, het vinden van een schoon paar sokjes in de kast en het samen smeren van een broodje chocopasta urgenter is dan het schrijven van een weergaloze passage voor het "schriftje". Mijn allergrootste dank gaat naar Gijs. Dank je wel voor alles, en met name voor je geduld en de ruimte die je hebt gegeven om dit proefschrift te kunnen schrijven.

Curriculum Vitae

Irma Hein was born on 20 January 1972 in Donderen (Drenthe, the Netherlands). She studied for a foundation degree in pharmacy at the Rijks University, Groningen and completed her medical training at the VU University, Amsterdam, in 2000. Subsequently she was a psychiatric resident at Meerkanten Mental Health Care, Ermelo, under supervision of drs. Piet Verhagen and dr. Harold van Megen; and then specialized in child and adolescent psychiatry at de Bascule Academic Center for Child- and Adolescent Psychiatry, Amsterdam, under supervision of prof. dr. Frits Boer and prof. dr. Theo Doreleijers. Since 2010 she is affiliated as a child and adolescent psychiatrist with Foundation Center 45, Diemen, the Dutch national institute for specialist diagnosis and treatment of psychotrauma complaints resulting from persecution, war and violence. She is engaged in outpatient-, day- and inpatient treatment of families and children who are refugees, asylum seekers or victims of human traffic. In 2011 she started at Academic Medical Center, Amsterdam, leading a research project granted by the Netherlands Organisation for Health Research and Development: *Development and use of a standardised instrument for assessing children's competence to consent in drug trials: are legally established age limits valid?* She participates in research collaborations with VUmc and LUMC, and will continue her work at the AMC. Irma is married to Gijs van Setten and they have three sons, Boris, Oscar en Kasper.

PhD Portfolio and Publications

1. PhD training (Workload in ECTS)

Courses

2011 Reference Manager Advanced (0.5)
2011 Scientific Writing in English (1.5)
2011 Practical Biostatistics (1.5)

Presentations

2014 Hein, I.M. Wilsbekwaamheidsbeoordeling ten aanzien van wijziging geslacht geboorteakte. Oral presentation, Center of Expertise on Gender Dysphoria, VUmc, Amsterdam. (0.5)

2014 Hein, I.M. Kan een kind onder de 12 jaar wilsbekwaam zijn? Oral presentation, Dutch Association of Pediatrics, Debate on childhood euthanasia, Utrecht (0.5)

2014 Hein, I.M. MacKiD studie; kunnen kinderen een weloverwogen beslissing nemen? Oral presentation, Congres klinisch onderzoek met kinderen, UMC Utrecht.(0.5)

2014 Hein, I.M., Dashorst, P., Mooren, T. Child in the shade of parental trauma. Poster presentation, International Symposium on the Impact of Great Wars and Beyond, Foundation Arq, Leiden. (0.5)

2014 Hein, I.M., Den Boer, J., Jasperse, A. Baby in beeld: vroege interventie bij getraumatiseerde moeders en hun zuigeling. Poster presentation, 42e NVvP voorjaarscongres, Maastricht. (0.5)

2014 Hein, I.M. Complex trauma en verstoord ouderschap; behandeling met Multifamily Therapy. Oral presentation, 42e NVvP voorjaarscongres, Maastricht. (0.5)

2014 Hein, I.M. Complex trauma en verstoord ouderschap; behandeling van kind en gezin. Oral presentation, Jaarcongres Artsen Jeugdgezondheidszorg Nederland, Utrecht. (0.5)

2011 Hein, I.M., De la Rie, S. Medische en ethische dilemma's in de behandeling van asielzoekers. Workshop, Jaarcongres Nederlandse Vereniging voor Psychotrauma, Amsterdam. (0.5)

2011 Hein, I.M. Can children decide to participate in research? Development of a standardized instrument to assess competence. Poster presentation, International Conference on Clinical Ethics and Consultation, VU University, Amsterdam. (0.5)

2011 De Ruijter, A.M., Boekbinder, J., Hein, I.M. Brainwiki, een digitale plek voor kennisuitwisseling met kinderen over kinderpsychiatrie. Workshop, 39e NVvP voorjaarscongres, Amsterdam. (0.5)

2008 G.C.E. Mauro, I.M. Hein, G.B. Van De Kraats. Psychotherapie en neurobiologie: the talking cure as neuronal therapy? Discussion Group, 36e NVvP voorjaarscongres, Amsterdam. (0.5)

2. Teaching

Lecturing, Tutoring, Mentoring

2012 3rd year medical students (0.5)
2013 3rd year medical students (0.5)
2nd year residents in Child and Adolescent Psychiatry (0.5)
2014 2nd year residents in Child and Adolescent Psychiatry (0.5)

3. Parameters of Esteem

Grants

2011 Development and use of a standardised instrument for assessing children's competence to consent in drug trials: are legally established age limits valid? ZonMw programma Ethische en juridische aspecten van geneesmiddelenonderzoek bij kinderen, €367.000,-.

4. Publications

Peer reviewed

Hein IM, Troost PW, Broersma A, de Vries MC, Daams JG, Lindauer RJL (2015). Why is it Hard to Make Progress in Assessing Children's Decision-Making Competence? *BMC Medical Ethics*, 16:1 doi:10.1186/1472-6939-16-1

Hein IM, Troost PW, de Vries MC, Knibbe CAJ, Goudoever JBv, Lindauer RJL (2015). Why do children decide not to participate in clinical research: a quantitative and qualitative study. *Pediatric Research*, accepted for publication.

Hein IM, Troost PW, Lindeboom R, Benninga MA, Zwaan CM, Goudoever JB van, Lindauer RJLL (2014). Accuracy of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) for Measuring Children's Competence to Consent to Clinical Research. *JAMA Pediatr.* 168(12):1147-53. doi:10.1001/jamapediatrics.2014.1694

Hein IM, Daams J, Troost PW, Lindeboom R, Lindauer RJL. (2014). Accuracy of assessment instruments for patients' competence to consent to medical treatment or research. *Cochrane Database Syst Rev.* (5). DOI: 10.1002/14651858.

Van Ee E, Hein IM, Bala J, Mooren T. (2014). Multifamily Therapy met vluchtelingen en asielzoekersgezinnen: van oorlog naar veiligheid. *Kind en Adolescent,* 35(3):205-215

Hein IM, Troost PW, Lindeboom R, de Vries MC, Zwaan CM, Lindauer RJ. (2012). Assessing children's competence to consent in research by a standardized tool: a validity study. *BMC Pediatr.* 2012 Sep 25;12:156. doi: 10.1186/1471-2431-12-156.

Hein IM, Huyser C. (2011). Antipsychotica in de behandeling van adolescenten met anorexia nervosa. *Psyfar* 2, 38-42.

Hein IM, Huyser C. (2010). Olanzapine in the treatment of adolescents with anorexia nervosa. Review. *Tijdschr Psychiatr.* 52(6):417-21.

Hein, I.M. (2008). Boekbespreking: Tegen de zon in kijken. Doodsangst en hoe die te overwinnen. *Tijdschrift Psychiatr.* 50(12):828 – 829.

Hein, I.M. (2004). Meeste misbruikte jongens worden geen dader. *Tijdschrift Psychiatr.* 46(4):259 – 259.

Hein, I.M. (2004). Schizofrenie vóór het 18e jaar: zijn er voorbodes, en wat zeggen deze? *Tijdschrift Psychiatr.* 46(8):570 – 570.

Submitted manuscripts

Hein IM, Troost PW, Lindeboom R, Goudoever JBv, Lindauer RJL. Key factors in children's competence to consent to clinical research.

Hein IM, Troost PW, Lindeboom R, Christiaans I, Grisso T, Goudoever JBv, Lindauer RJL. Assessing Children's Competence to Consent to Predictive Genetic Testing.

Hein IM, de Vries MC, Troost PW, Meynen G, Lindauer RJL, van Goudoever JB. Informed consent instead of assent is appropriate in children from the age of twelve.

Grootens-Wiegers P, Hein IM, van den Broek JM, de Vries MC. Child development and the neuroscience of medical decision-making.

Jasperse, A., Den Boer, J.C., Hein, I.M. Geboren uit verkrachting; trauma versus onschuld. Dilemma's in de zoektocht naar hechting.

Other

Hein IM. Jonge kinderen kunnen ook wilsbekwaam zijn. Kinderarts en Samenleving, 2014 mei, 18-19, NVK.

Hein IM. Wilsbekwaamheid bij kinderen, Hoofdstuk 3, Richtlijn Zorgvuldigheidscriteria bij onderzoek, NVK, under review.

Lay Media
Newspaper/magazine articles
Kind snapt nut van medisch onderzoek. Dagblad Trouw, 18 October 2014

AMC toetst beslisvaardigheid kinderen bij medische beslissingen, Dagblad Het Parool, 27 July 2014
http://www.parool.nl/parool/nl/4/AMSTERDAM/article/detail/3699631/2014/07/27/AMC-toetst-beslisvaardigheid-kinderen-bij-medische-beslissingen.dhtml

AMC ontwikkelt meetmethode voor wilsbekwaamheid kinderen, NRC Handelsblad, 21 July 2014
http://www.nrc.nl/nieuws/2014/07/21/amc-ontwikkelt-meetmethode-voor-wilsbekwaamheid-kinderen/

Ook een kind kan wilsbekwaam zijn, NRC Handelsblad, 21 July 2014
http://www.nrc.nl/handelsblad/van/2014/juli/21/ook-een-kind-kan-wilsbekwaam-zijn-1404044

Wikken en wegen op je negende. AMC Magazine, March 2011

Television
Wanneer is een kind wilsbekwaam? Eenvandaag TV, 13 October 2014
http://www.eenvandaag.nl/gezondheid/54528/wanneer_is_een_kind_wilsbekwaam_?autoplay=1

Radio
Zijn kinderen wilsbekwaam? Eenvandaag Radio, 10 September 2014
http://www.eenvandaag.nl/binnenland/53790/zijn_kinderen_wilsbekwaam_

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