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Decision-making in severe traumatic brain injury: patient outcome, hospital costs, and research practice

Dijck, J.T.J.M. van

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Author: Dijck, J.T.J.M. van

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CHAPTER 8

Informed consent procedures in patients with an acute inability to provide informed consent: policy and practice in the CENTER-TBI study

Authors:

Roel P.J. van Wijk^{1*},
Jeroen T.J. M. van Dijck^{1*},
Marjolein Timmers²,
Ernest van Veen^{2,3},
Giuseppe Citerio^{4,5},
Hester F. Lingsma³,
Andrew I.R. Maas^{6,7},

David K. Menon⁸,
Wilco C. Peul¹,
Nino Stocchetti^{9,10},
Erwin J.O. Kompanje^{2,11},
The CENTER-TBI investigators and participants
*Contributed equally to the study

Affiliations:

1. University Neurosurgical Center Holland, LUMC, HMC & Haga, Leiden & The Hague, the Netherlands.
2. Department of Intensive Care, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.
3. Centre for Medical Decision Making, Department of Public Health, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.
4. School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy. OrcidID 0000-0002-5374-3161.
5. San Gerardo Hospital, ASST-Monza, Italy.

6. Department of Neurosurgery, Antwerp University Hospital, Edegem, Belgium.
7. University of Antwerp, Antwerp, Belgium.
8. Department of Anaesthesia, University of Cambridge, Cambridge, United Kingdom.
9. Department of Physiopathology and Transplantation, Milan University, Milan, Italy.
10. Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano, Milan, Italy.
11. Department of Medical Ethics and Philosophy of Medicine, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.

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ABSTRACT

Purpose: Enrolling traumatic brain injury (TBI) patients with an inability to provide informed consent in research is challenging. Alternatives to patient consent are not sufficiently embedded in European and national legislation, which allows procedural variation and bias. We aimed to quantify variations in informed consent policy and practice.

Methods: Variation was explored in the CENTER-TBI study. Policies were reported by using a questionnaire and national legislation. Data on used informed consent procedures were available for 4498 patients from 57 centres across 17 European countries.

Results: Variation in the use of informed consent procedures was found between and within EU member states. Proxy informed consent (N=1377;64%) was the most frequently used type of consent in the ICU, followed by patient informed consent (N=426;20%) and deferred consent (N=334;16%). Deferred consent was only actively used in 15 centres (26%), although it was considered valid in 47 centres (82%).

Conclusions: Alternatives to patient consent are essential for TBI research. While there seems to be concordance amongst national legislations, there is regional variability in institutional practices with respect to the use of different informed consent procedures. Variation could be caused by several reasons, including inconsistencies in clear legislation or knowledge of such legislation amongst researchers.

Keywords: Traumatic brain injury; Informed consent; European union; Ethics.

BACKGROUND

Patient informed consent is one of the basic principles underpinning clinical research. Patients have the right to be informed about a proposed study and should have the opportunity to make an autonomous decision on study participation. It is however impossible to obtain patient informed consent from patients with an acute inability to provide informed consent due to an acute illness such as traumatic brain injury (TBI).¹ Research with TBI patients is however essential to optimize treatments and improve patient outcome. Therefore, several pragmatic alternatives are available in case patient informed consent could not be obtained.²

Proxy informed consent is the most frequently used alternative. Close family members or unrelated appointed legally authorized representatives are selected in accordance with applicable national or local regulations. These so-called proxies have the legal right to provide informed consent on behalf of the patient.³ Proxies are however often unavailable in the acute setting or are unable to make a valid judgment for several other reasons.⁴⁻⁹ This is especially complicated in emergency research where time is scarce.

To overcome this, some research settings allow an independent physician to decide on behalf of the patient. In many European countries, it is also accepted to include and randomize patients in emergency research settings without prior patient- or proxy informed consent and ask consent for study continuation later (deferred consent procedure).^{3,10} Researchers can also use the so-called 'exception from consent' and 'waiver of consent' procedures, which allow study start without prior patient- or proxy informed consent without the requirement of informed consent for study continuation.^{11,12}

The relative pros and cons of different informed consent procedures have led to substantial regulatory variation within and between European Union (EU) Member States and globally.^{13,14} The EU has replaced the Data Protection Directive and the Clinical Trials Directive by the General Data Protection Regulation and the Clinical Trials Regulation to harmonize informed consent procedures.^{3,15-17} Unfortunately, neither regulation addresses the specific situations of patients with an acute inability to provide informed consent in detail, and neither clearly differentiates between acute or chronic mental conditions. Although the General Data Protection Regulation provides

for exemptions from patient informed consent procedures for observational research by leaving room for national legislation, informed consent in clinical emergency research is not mentioned in national law in 12 EU Member States.^{13,18}

The lack of clear directions in European and national legislation may be expected to result in substantial practice variation in consent procedures for patients with an acute inability to provide informed consent.¹⁹ The use of different informed consent procedures in international multi-center studies could cause recruitment inefficiency, non-homogenous patient inclusion, selection bias, asymmetrical randomisation, and limited external validity of study results.^{20,21} Clearly, optimization of informed consent procedures and harmonization of regulations is important for future research initiatives.

The aim of this study is to inform researchers and policymakers on the use and challenges of informed consent procedures in a large prospective observational study including patients with an acute inability to provide informed consent due to TBI. Therefore, we investigated local policy and observed practice of informed consent procedures in the Collaborative-European-Neuro-Trauma-Effectiveness-Research in Traumatic Brain Injury (CENTER-TBI) study.²²

MATERIALS AND METHODS

CENTER-TBI and study sample

The CENTER-TBI project includes a large prospective observational study on TBI conducted in 63 neurotrauma centres across Europe and Israel.²⁰⁻²¹ CENTER-TBI had a follow up period of 12 to 24 months and required extra blood samples and, in a subpopulation, MRI scans in addition to standard care. For this particular study, we excluded four centres with low inclusion rates (<five patients) and 2 centres from Israel, because we focussed on European centres. All remaining centres (N=57) from 17 European countries obtained IRB approval and were analyzed. (See Suppl Table 1).

Policy: Provider profiling and national legislation

Investigators of each study center completed “Provider Profiling” questionnaires prior to recruitment to the CENTER-TBI Core study. The questionnaires aimed to characterize general healthcare processes and, specifically for this present study, the use of informed consent procedures. (see Suppl file 1). These questions were about the acceptance and

use of informed consent procedures in general and not specifically for the CENTER-TBI study. The question mentioning the 'deferred consent/waiver of consent' alternatives was used to assess the possibility of study start without prior informed consent in emergency research and was named deferred consent in this article. Answers explicitly represent a general consensus at the centres, rather than an individuals' preference, in an attempt to capture the actual policy of all study centres. Responses were collected and stored by using a secure online database (QuesGen Systems Incorporated, Burlingame, CA, USA).²³ Detailed information on the provider profiling questionnaires has been published previously.²⁴ An additional analysis of national regulations that were applicable at the time of study was performed and compared with the results of the questionnaire and actual observed informed consent procedures.¹³

Practice: CENTER-TBI Core study

The CENTER-TBI Core study (clinicaltrials.gov NCT02210221; RRID: SCR_015582) was conducted between December 2014 and December 2017.²⁵ Enrolment criteria were a clinical diagnosis of TBI, indication for CT-scanning, and presentation to study centre within 24h of injury. Approval from an IRB or any other appropriate ethics review body was obtained by all centres and informed consent procedures followed local and national requirements. On enrolment, patients were differentiated by care pathway: ER stratum (discharged from emergency room), Admission stratum (hospital ward), and ICU stratum (admission to the intensive care unit (ICU)). For this study, informed consent practice was pragmatically observed in the ICU stratum (N=2137) of CENTER-TBI, since we focussed on patients with an acute inability to provide informed consent. The presence of the inability to provide informed consent was very unlikely in patients from the ER and Admission stratum because nearly all sustained mild TBI and provided informed consent themselves.

Clinical data included details on the type and time of informed consent and were collected and de-identified using a web-based electronic case report form (QuesGen) and stored on a secure database, hosted by the International Neuroinformatics Coordinating Facility (INCF; www.incf.org) in Stockholm, Sweden.²⁶

Analyses

Data (Version 1.0, released: 01/11/2018) was extracted via the custom-made data access tool Neurobot (<http://neurobot.incf.org>), developed by INCF. Descriptive statistics were used to obtain frequencies and percentages. For analysis of potential differences

between regions we grouped countries into six regions based on the United Nations geo-scheme (See Suppl Table 1).²⁷ Due to the agreed anonymity of participating sites, it was not always possible to display all differences between countries, as some countries have only 1 or 2 participating sites. Potential differences between centres in one country were analyzed in countries with three or more participating centres. Analyses were performed using R version 3.6.0.

RESULTS

All 57 participating centres completed the provider profiling questionnaire. The majority was completed by principal investigators and medical professionals (N=20), IRB members (N=15), and staff members (N=13). (See Suppl Table 2) Most centers were academic hospitals (91%) with a designation as Level I trauma centre (68%). Thirty (53%) centres had a department of medical ethics and 28 (49%) had extensive neurotrauma research experience, with five or more research applications over the previous five years. (See Suppl Table 3)

Policy

Alternatives for patient informed consent were widely accepted. (Table 1 & Fig 1). Most IRBs allowed the use of proxy informed consent (79%) for acutely mentally incapacitated patients, while consent by an independent physician was less frequently allowed (37%). The majority of centers considered deferred consent (82%) for emergency research to be a valid alternative.

Table 1. Number of study centres (%) that allow the use of an informed consent procedure in acutely mentally incapacitated patients.

Informed consent procedure	Yes N (%)	No N (%)	Unknown N (%)
Proxy informed consent	45 (79)	11 (19)	1 (2)
Consent by an independent physician	21 (37)	30 (53)	6 (10)
Deferred consent	47 (83)	7 (12)	3 (5)

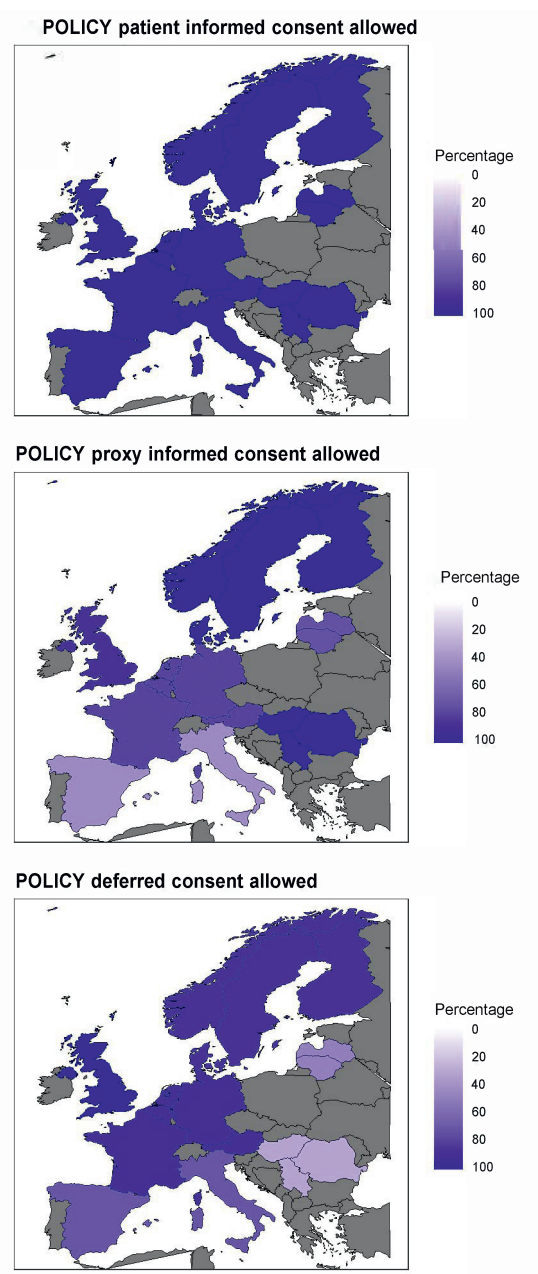


Figure 1: Reported policy on types of consent in acutely mentally incapacitated patients in Europe. (Percentage of centres in one country that allow the type of consent in the questionnaire)

Substantial variation in informed consent policies was noted between regions in Europe. All centres in Northern and Eastern Europe reported prior proxy informed consent to be valid (100%), in contrast to centres in The Baltic States (75%), Southern Europe (45%), the United Kingdom (UK) (89%) and Western Europe (81%). Regarding Southern Europe, especially Italian centers (62%) reported proxy informed consent to be invalid. (See Suppl Table 4).

Acceptance of consent by an independent physician was lower (37%) and variable across European regions. (See Fig. 1 & Suppl Table 4) It was especially considered valid in Germany (100%), the UK (89%), and Spain (67%). None of the centers from The Netherlands, Italy and Norway reported this alternative to be valid, while other countries were inconsistent. (see Suppl Table 5)

The use of the deferred consent procedure was reported valid by most centers in most regions, except Eastern Europe. (see Suppl Table 4) When reported valid, it was mostly regulated by IRB approval (N=36) or by law (N=11). Of countries with ≥ 3 centres, all mentioned that the procedure was valid. (see Suppl Table 5)

Practice

Overall practice

All participating centres (N=57) included 4498 patients. Most patients were admitted to the ICU stratum (N=2137;48%) followed by the Admission stratum (N=1517;34%) and the ER stratum (N=844;19%). Overall, patient informed consent (N=2497;56%) was the most frequently used type of consent, followed by proxy informed consent (N=1635;36%) and deferred consent (N=366;8%) The use of patient informed consent was lower for patients requiring ICU admission (N=426;20%) compared to patients requiring admission to the ward (N=1266;83%). (Table 2)

Table 2. Number of patients (%) and type of used informed consent procedure per stratum in the CENTER-TBI study.

Consent type Stratum	ER (N=844, 19%)	Admission (N=1517, 34%)	ICU (N=2137, 48%)
Patient informed consent (N=2497, 56%)	805 (95)	1266 (83)	426 (20)
Proxy informed consent (N=1635, 36%)	35 (4)	223 (15)	1377 (64)
Deferred consent (N=366, 8%)	4 (0.5)	28 (2)	334 (16)

Practice in ICU stratum

Proxy informed consent (N=1377;64%) was the most frequently used type of consent in the ICU, followed by patient informed consent (N=426;20%) and deferred consent (N=334;16%) (Table 3). Proxy informed consent was most frequently used in the UK (96%), Southern Europe (80%) and The Baltic States (76%), and less frequently in Northern (56%) and Western Europe (49%). In contrast, deferred consent was most frequently used in Northern (19%) and Western Europe (25%) but infrequently in the UK (0.3%) and the Baltic States (3%) (Table 3). Seven countries (41%) did not use deferred consent. Austria did not use proxy informed consent, but showed the highest number of deferred consents instead (65%). (see Suppl Table 6)

Table 3. Number of patients (%) and type of used informed consent procedures in the ICU stratum per region.

Answers Regions	Sample Total (N=2137)	Baltic States (N=33)	Eastern Europe (N=33)	Northern Europe (N=391)	Southern Europe (N=546)	United Kingdom (N=271)	Western Europe (N=863)
Patient informed consent	426 (20)	7 (21)	11 (33)	97 (25)	75 (14)	10 (4)	226 (26)
Proxy informed consent	1377 (64)	25 (76)	20 (61)	219 (56)	433 (79)	260 (96)	420 (49)
Deferred consent	334 (16)	1 (3)	2 (6)	75 (19)	38 (7)	1 (0.3)	217 (25)

Comparison of policy and practice

Proxy informed consent and deferred consent procedures are accepted by national legislation of all displayed countries.^{13,28,29} (Table 4) Some centers however reported proxy or deferred consent procedures to be not accepted. In addition, there was variation between accepted procedures and actually used informed consent procedures. Italy for instance reported a low rate of proxy informed consent acceptance and a high enrolment rate using proxy informed consent.

When also including countries (≤ 3 centres) that could not be displayed, the use of deferred consent in emergency situations was allowed in 10 out of 17 countries. The procedure was not mentioned in national legislation in 6 countries. In the questionnaire, 47 (82%) of the participating centres reported that it was possible to include patients with an acute inability to provide informed consent by using deferred consent. In practice, only 15 centres from seven countries were responsible for 99% (N=330) of the deferred consent cases in the ICU.

Table 4. Comparison of observed practice, national legislation and reported policy regarding informed consent procedures in the CENTER-TBI ICU stratum.

Country (N)	Patients included using patient informed consent (N (%))	Proxy informed consent procedures accepted according to national legislation? [13]	Number of centers (%) accepting proxy informed consent according to provider profiling
Belgium (N=4)	71 (37)	Yes	4 (100)
France (N=5)	25 (22)	Yes	5 (100)
Germany (N=4)	24 (28)	Yes	2 (50)
Italy (N=8)	34 (10)	Yes	3 (37)
Netherlands (N=7)	68 (19)	Yes	6 (86)
Norway (N=3)	33 (20)	Yes [28]	3 (100)
Spain (N=3)	41 (21)	Yes	2 (67)
UK (N=9)	10 (4)	Yes	8 (89)
Total	306		33

DISCUSSION

Patient informed consent alternatives like proxy informed consent, deferred consent and independent physician consent were widely used in the CENTER-TBI study and were essential to include ICU admitted TBI patients with an acute inability to provide informed consent. Alternatives to patient informed consent are essential in TBI research. Only 20% of ICU patients provided patient informed consent. This study found substantial between and within-country variation in reported accepted informed consent policies and actually used informed consent procedures. Variation could be caused by several reasons and could indicate that either clear national or European legislation is unavailable or that knowledge of such legislation may be inconsistent amongst clinicians and researchers.

The number of patient informed consent (N=2497; 56%) observed in the CENTER-TBI core study was higher than expected. This was partly due to the large number of patients in the ER and Admission strata (>95% with mild TBI) that were able to provide informed consent (87%). In addition, many patients in the ICU stratum had mild TBI (36%).²⁷ This could explain the high number of patient informed consents (20%) in the ICU, but it is also possible that study personnel wrongly considered a patient to have the ability to provide patient informed consent. The CENTER-TBI study did not use or document any assessment of a patients' ability to provide informed consent. Although assessment methods are available and used in some studies, they have important limitations.^{30,31} It is important that researchers formally assess the ability to provide informed consent in all patients when possible. Especially in patients with a

Patients included using proxy informed consent (N (%))	Deferred consent accepted in emergency research according to national legislation? [13]	Number of centers (%) accepting deferred consent in emergency research according to provider profiling	Patients included using deferred consent (N (%))
122 (63)	Yes	4 (100)	0 (0)
90 (78)	Yes	5 (100)	0 (0)
54 (62)	Yes	3 (75)	9 (10)
279 (79)	Yes	5 (63)	38 (11)
154 (43)	Yes	6 (86)	137 (38)
94 (58)	Yes [29]	3 (100)	36 (22)
154 (79)	Not mentioned	3 (100)	0 (0)
260 (96)	Yes	9 (100)	1 (0.4)
1207		38	221

possible episode of an acute inability to provide informed consent. This assessment should ideally be recorded in the case report form to guarantee the validity of patient informed consent.

Alternatives for patient informed consent allowed the inclusion of 80% of ICU stratum patients. Overall, proxy informed consent was the most frequently used alternative. Although it was not always reported to be an accepted informed consent policy for mentally incapacitated patients, it was an accepted procedure by all national laws. Proxies usually prefer to be involved in decision-making, but proxy informed consent has several important limitations.³² Several studies report substantial discrepancies between patients and proxies and conclude that proxies are poor surrogate decision-makers.^{7-9,33} In addition, proxies are not always present in emergency situations, or are too overwhelmed by the stressful situation to provide valid proxy informed consent.^{34,35} Researchers and clinicians should be aware of the many factors that are important in the process of informed consent.³⁶

Fortunately, it was also possible to include patients by using deferred consent when it was impossible to obtain prior patient or proxy informed consent. A total of 45 centres (79%) from ten countries, according to national law, or 47 centres (82%), according to reported policies, were allowed to use this procedure. Nonetheless, only 15 centres (26%) actively (>2 inclusions) used it. There are multiple explanations for this discrepancy. First, the use of deferred consent might be accepted in national legislation, but local IRBs may not have authorised it for the CENTER-TBI study. Also, the use of deferred consent is not ethically neutral and the acceptance by IRBs, healthcare providers, patients and relatives

differ substantially.³⁷⁻⁴² Second, deferred consent was authorised as valid, but its use was not required because proxy or independent physician consent were used. Last, it is also possible that local researchers were unaware of the possibility of deferred consent.

Current European regulations include The Data Protection Directive and the Clinical Trials Directive, which were applicable at the time when patients were included in CENTER-TBI, are or will be superseded by the General Data Protection Regulation and the Clinical Trial Regulation respectively. However, since the General Data Protection Regulation does not apply to anonymized data and alternatives to patient informed consent are left to the legislation of Member States, large improvements in harmonization are not expected.^{19,43} The Clinical Trials Regulation does state that patient informed consent may be deferred in some specific situation and might thereby cause an increase in the use of deferred consent.^{17,19,44-46}

There is a lack of clear regulations on emergency research in mentally incapacitated patients and lack of harmonization regarding informed consent procedures in European Neurotrauma centres. Performing multinational trials is challenging when variations in acceptance of alternatives for patient informed consent exist.^{14,47} Potential issues not only include IRB processing and patient recruitment inefficiency and therefore study delay, but also non-homogenous patient inclusion, selection bias, asymmetrical randomisation, and limited external validity of study results.^{20,21} Although informed consent procedures are bound by national laws, institutional regulations and cultural factors, it could be beneficial for future research initiatives to harmonize procedures and regulations.

This study has several limitations. First, the majority of the participating centres were academic centres specialized in research and neurotrauma resulting in a possible selection bias. Second, by pragmatically focusing on patients from the ICU stratum with the highest likelihood of an inability to provide informed consent, we might have missed a few patients that were included in the ER or ward stratum. Unfortunately, there was no registered formal assessment of the ability to provide informed consent that could have been used to identify patients. Third, in addition to an analysis of national laws, reported informed consent policies were based on the provider profiling questionnaire rather than on actual policies. Although most responses were provided by seniors, the discrepancies could be caused by provider profiling errors due to variable individual understanding of actual policies and/or regulations. It could however also reflect the centres' general consensus or IRB specific directives rather

than national juridical policies. Fourth, it is important to bear in mind that CENTER-TBI is an observational study, although IRBs in three countries considered it to be an interventional study as blood samples were requested. Results on consent policy and practice might be different for interventional studies or randomized controlled trial. This is because the consequences of participation might be bigger and effective retrospective refusal of study participation is not possible as study interventions have already taken place. Although our data are derived from a patient population with TBI, the identified problems and insights have relevance for other conditions that could cause an inability to provide informed consent.

CONCLUSIONS

Alternatives to patient informed consent are essential for studies including TBI patients with an acute inability to provide informed consent. The substantial variation in reported and used informed consent procedures in Europe could be caused by several reasons and could indicate that clear national or European legislation is unavailable or that knowledge of such legislation may be inconsistent amongst clinicians and researchers. Future research initiatives could benefit from clear and harmonized regulations for this subcategory of patients.

HIGHLIGHTS

1. Variation is reported in consent procedures between and within European countries.
2. Discordance between reported consent policy and observed practice was common.
3. Deferred consent was accepted in many countries, but not frequently used.
4. Harmonisation of consent procedures is needed to improve research efficiency.
5. Researchers should verify and document a patients ability to provide informed consent.

Supplementary files

Available online: <https://doi.org/10.1016/j.jcrc.2020.05.004>

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