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JAMDA 24 (2023) 541–547

JAMDA

journal homepage: www.jamda.com

Original Study

Proxy Decision-Making for Clinical Research in Nursing Home Residents with Dementia: A Qualitative Analysis

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Keywords:
Dementia
nursing home
proxy decision-making
qualitative study
randomized controlled trial
research

A B S T R A C T

Objectives: The benefit-risk ratio of many interventions remains unclear in older adults with dementia. Efforts for more representative trial inclusion are made; however, recruiting and particularly gaining informed consent remains complex. For research participation, dementia compels the designation of a legal guardian (LG) to give proxy consent. To advance future trial development, we aimed to provide more insights into the factors that affect the proxy decision-making process in dementia research.

Design: A qualitative analysis of semi-structured interviews about proxy decision-making on participation in dementia research.

Setting and Participants: LGs of nursing home residents that gave (n = 19) and refrained from giving (n = 18) proxy consent for a clinical trial (the Danton study) in the Netherlands.

Methods: Verbatim transcripts were thematically analyzed by using a preliminary deductive framework with room for induction of additional emerging themes, being an overall abductive approach. Based on that theme list, related factors of the decision-making process were grouped into overarching levels and merged into a step-by-step process.

Results: When discussing proxy decision-making on the participation of an older adult with dementia in a clinical trial, LGs described interconnected factors on the level of the study and patient. Past experiences and attitudes of the LG influenced the weighing of these study- and patient-related factors, leading to a preliminary decision. Other proxies and treating health care professionals (HCPs) were named as important other stakeholders of the decision-making process.

Conclusions and Implications: When giving proxy consent for research participation, LGs weigh study- and patient-related factors, leading to an initial benefit-risk evaluation. This weighing process is influenced by LG-related factors and can be modulated by other proxies or treating HCPs, leading to a definitive decision. Although insights into these underlying mechanisms could facilitate the proxy decision-making process for both LGs and researchers, treating HCPs could act as an independent party.

The management of most chronic health conditions in the geriatric population is based on evidence from randomized controlled trials (RCTs). Because of the exclusion criteria of these trials, older adults with multimorbidity, limited life expectancy, and cognitive impairment are frequently not enrolled.[1-4] Consequently, the overall benefit-risk ratio of many prescribed drugs remains questionable in older patients with multimorbidity and/or cognitive impairment.[1,5,6] Especially older adults with dementia, who are both at an increased risk for prescription of a potentially inappropriate drug and an associated

This study was supported by a grant from the research and innovation program "Memorabel," the Netherlands Organisation for Health Research and Development (ZonMw project number 733050835). All researchers worked independently from the funders. The sponsor did not have a role in the design, methods, data collection, analysis, and preparation of the article.

The authors declare no conflicts of interest.

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https://doi.org/10.1016/j.jamda.2023.02.017

adverse health outcome,[7] could benefit from more evidence-based treatment strategies.

Efforts are being made to better represent the whole population of older adults in clinical trials[8]; however, the recruitment and informed consent procedure for RCT participation of particularly older adults with dementia remain complicated.[9] At an advanced stage, cognitive impairment interferes with an individual's mental capacity to perform decision-making tasks, compelling the designation of a legal guardian (LG). In the context of study participation, this results in the need for both assent of the patient and proxy consent of the LG.[10]

With a need for RCTs on the management of chronic health conditions in older adults with dementia and a complicated informed consent procedure, a key question is how proxy decision-making on participation in a clinical trial unfolds in real life. Therefore, this qualitative analysis explored which factors play a role in decision-making on behalf of patients with dementia to participate in an RCT on the deprescribing of antihypertensive treatment. More insights into this process could advance future trial development and will lead to more successful research in older adults with dementia.

Methods

Design and Setting

This qualitative analysis was conducted alongside the enrollment and follow-up phase of an RCT, being the Danton study. The overarching primary objective of this RCT was to investigate whether a gradual increase in blood pressure, by stepwise discontinuation of antihypertensive treatment, reduces neuropsychiatric symptoms and improves the quality of life in older nursing home (NH) residents with dementia (WHO-ICTRP-ID-NTR [Netherlands Trial Register ID: NTR7573]).

After an eligibility screening by the local elderly care physician (an NH-affiliated practitioner specialized in medical care for frail older adults), a list of potential trial subjects was composed. Based on that list, LGs of selected NH residents received an information letter and a preliminary consent form, explaining the purpose, procedures, and possible hazards of the trial. In case of additional questions, LGs could discuss trial participation with the elderly care physician (fully aware of the resident's medico-social context) or contact the coordinating research center. LGs were invited to return the preliminary consent form, either with a proxy consent for participation or with a response card with a reason for refusal. If the coordinating research center received a consent form, a study nurse confirmed it by telephone, leading to the inclusion of a new trial subject.

Ethical Approval

This qualitative substudy of the Danton study (MEC-Protocol-ID-NL65719.058.18) was approved by the Medical Ethical Committee Leiden-Den Haag-Delft (Leiden, The Netherlands). All participating LGs gave verbal informed consent recorded on tape.

Participants

In the Netherlands, guardianship duties are usually performed by spouses, siblings, or close friends after designation by the district judge. When this is not possible, an external LG drawn from a panel of volunteers (a volunteer LG) can be appointed. To fully explore the proxy decision-making process, all types of LGs, including those who refrained from trial participation of their relative/ward, were eligible for an interview.

Legal guardians who gave proxy consent (consenting LG)

All LGs of the 20 trial subjects who finished the trial in June and July 2020 (being 8 months after proxy consent) were invited for an interview. Because all LGs agreed to be interviewed, this resulted in 19 interviews (1 interviewee was LG for 2 trial subjects).

Legal guardians who did not give proxy consent (refraining LG)

Between July 2020 and April 2021 (second wave of enrollment), we invited 589 LGs for participation of their relative/ward in the Danton study. We received 155 response cards with reasons for refusal, of which 28 included a telephone number. Of those 28 LGs, 10 were not available by phone or were not willing to participate, leading to 18 interviews.

Data Collection

Based on multiple focused discussions with members of the Older Persons Advisory Board Care & Well-being South Holland North (Supplementary Table 1) and 6 semi-structured interviews with LGs from our professional network (Supplementary Table 2), a preliminary framework and corresponding interview guide (Supplementary Tables 3 and 4) was developed. This interview guide formed the roadmap for the semi-structured interviews of our qualitative analysis. First, the decision-making process was discussed with a focus on arguments in favor or against trial participation of the patient (ie, the NH resident), whereafter this was compared with experiences and opinions concerning self-decision-making on research. Second, the physician's role, the informed consent procedure with signature obtainment, and insurance documentation were addressed. Interviews were concluded with the patient's past perspectives and attitudes concerning research. JMKB, a coordinating researcher-physician of the Danton study, conducted all interviews between June 2020 and June 2021. Interviews were done by telephone, recorded on audiotape, and lasted on average 28 minutes (range 12–51 minutes).

Data Analysis

Audiotapes were anonymized, chronologically numbered, and transcribed verbatim by a professional transcription provider. After all interviews were done, transcripts were thematically analyzed,[11] by using a preliminary deductive framework from the preceding focus groups, with room for induction of additional emerging themes, being an overall abductive approach.[12] Initially, 2 researchers (JMKB and LAW) independently coded the first 4 interviews with consenting LGs. After code-by-code comparing that led to a joint coding system, the remaining interviews were coded independently. Next JMKB and LAW created a theme list based on the individual codes. The complete coding results and initial theme list were discussed with RKEP, a general practitioner (GP) with expertise in qualitative research. Based on that theme list, related factors that guided decision-making were grouped into overarching levels of the process and combined into a new framework. Afterward, the whole process was repeated for the interviews with refraining LGs. In multiple meetings with all authors, including 2 GPs and an elderly care physician, both separate frameworks were compared, reviewed, and merged into a step-by-step process. Despite the number of interviews being determined by the maximum available, thematic saturation was reached before encoding all interviews. All remaining interviews were used for confirmation. QDA miner lite was used for coding (version 2.0.8., Provalis Research). Quote selection was done by JMKB and LAW, whereafter they were translated (Dutch-to-English) by an independent bilingual medical editor-translator.

Results

Interviewed Legal Guardians

Nineteen consenting LGs (median age 68.5 years; 32% women) and 18 refraining LGs (median age 62.0 years; 67% women) were interviewed. Although most interviewees were first-degree relatives, 5 (3 consenting, 2 refraining) of the 37 interviewees were not related by blood or marriage with the NH resident (see Table 1).

Main Levels

Discussing proxy decision-making on RCT participation exposed factors that could be grouped into 3 overarching levels. The first subset of factors was on the level of the study, the second on the level of the patient (ie, the NH resident), and the third on the level of the LG him/herself.

Factors on the level of the study

Three factors connected to the study and its design were relevant for the proxy decision-making process.

Aim and hypothesis. Consenting LGs took a positive view toward the proposed mechanism of action of the trial intervention and were interested in its potential effect. By contrast, refraining LGs were skeptical about the effect measurability of the intervention on the predefined outcome.

> **YES-09**: *"In addition, for me personally it was interesting to see that due to the increase in blood pressure, blood travels faster through your body. And that this might lead to something for her [his mother], that she could communicate a bit better."*
>
> **NO-07**: *"...the sort of questions, the ones you could ask to determine whether or not the treatment regime has any influence on her [his mother] deterioration. I was really wondering, how on earth are you going to measure that?"*

Burden. Regardless of the fact whether consent was given and independent of the potential risk, the study-related burden for the patient played a role in the decision. The discourse diverged in how the LG assessed the study-specific burden. For some LGs, the low study-specific burden convinced them to give consent.

> **YES-11**: *"Oh, taxing? No, it's important that it isn't overtaxing. Then it's easier to reach a decision. If you'd said, you need a whole bunch of physical examinations, or made all sorts of unexpected demands, then you could expect a lot of people to drop out sooner."*

Other LGs preferred to avoid every potential burden, even if the patient would hardly be aware of trial participation.

> **NO-02**: *"No. I'm just going to be very Dutch: we don't want a whole performance with my mother's body. I haven't even discussed it with the others yet."*
>
> **NO-15**: *"She's 85, she [her mother-in-law] won't live forever, so to burden her with this now… She won't understand that much herself, but she's 85; we want her to live the years she's still with us in peace."*

One volunteer LG acknowledged the necessity of science for medical progress but mentioned her limited amount of time for participation in research.

> **NO-05**: *"I also benefit from scientific research, that's where improvements in medical understanding come from. But I read here that informal carers have to complete a questionnaire 3 times, and I just don't have the time."*

Risk. The third, and most discussed, factor related to the study was the risk associated with the investigated intervention. Consenting LGs judged the risk of participation as manageable and were assured that in case of adverse events, one would intervene.

> **YES-19:** *"We didn't feel like, you know, there would be any negative consequences for my father. We really felt, well, just let them give it a go. And even if he ends up in the group with tapered off medicines, we wouldn't object to that either. And if it were to get too high, we assume action would be taken."*
>
> **YES-08:** *"What was important was that there were assurances, that if things were to go wrong then they would intervene."*

Refraining LG, on the other hand, evaluated the effects of the investigated intervention as hazardous. Besides the potential risk of the intervention, a lack of confidence in proper control during the intervention, led in some cases to refrain from giving consent.

Table 1
Demographic Characteristics of Interviewed LGs

Consenting LGs (n = 19)				Refraining LGs (n = 18)			
ID	Sex	Age	Relation to NH Resident	ID	Sex	Age	Relation to NH Resident
YES-01	M	81	Spouse	NO-01	M	89	Spouse
YES-02	M	73	Volunteer LG	NO-02	F	67	Daughter
YES-03	F	n/a	Daughter	NO-03	F	58	Daughter
YES-04	M	76	Spouse	NO-04	F	65	Daughter
YES-05	M	62	Son	NO-05	F	56	Volunteer LG
YES-06	F	n/a	Daughter-in-law	NO-06	F	62	Daughter
YES-07	M	60	Son	NO-07	M	66	Son
YES-08	F	48	Volunteer LG	NO-08	M	75	Spouse
YES-09	M	57	Son	NO-09	F	62	Daughter-in-law
YES-10	M	75	Spouse	NO-10	M	66	Son
YES-11	F	n/a	Daughter-in-law	NO-11	M	53	Brother-in-law
YES-12	M	50	Son	NO-12	M	54	Son
YES-13	F	67	Daughter	NO-13	F	78	Spouse
YES-14	M	70	Nephew	NO-14	F	63	Daughter
YES-15	M	83	Brother	NO-15	F	40	Daughter-in-law
YES-16	M	n/a	Son	NO-16	F	50	Daughter
YES-17	M	55	Volunteer LG	NO-17	F	58	Daughter-in-law
YES-18	M	86	Brother	NO-18	F	52	Volunteer LG
YES-19	F	n/a	Daughter				

F, female; M, male; n/a, not available.

NO-04: *"I am going to be brief, I'm just not going to risk her [her mother] health, she has an enormously high blood pressure already, and that's that."*

NO-09: *"It's a bit awkward to mention, but I'll say it anyway - I'm not really satisfied with the way the nursing home is managing things. Because quite a few medical aspects, I feel, are not going as I'd like ... And I found the situation that the carers had to measure blood pressure and keep an eye on my mother [her mother-in-law] quite troubling."*

Factors on the level of the patient

Four factors related to the patient (the eligible NH resident) emerged as relevant in the process of proxy decision-making.

Past attitudes. The patient's past attitudes played a significant role in the process. Although multiple LGs named the patient's positive feelings about research, one interviewee mentioned her mother's statements about being a "guinea pig."

YES-12: *"If she [his mother] could participate in something that would help advance any sort of research, she would have been really in favor of it. I am sure of that."*

NO-16: *"Then my mother said: 'If it ever comes to it, I'd really rather not take part, I don't want to be a guinea pig...'"*

Expression. Some LGs tried to discuss study participation with the patient. Besides attitudes in the past, certain patients were capable of expressing their opinions on the current study. They trusted their LG and did not oppose participation.

YES-07: *"She [his mother] said, take a look, if you all think it's a good thing, then I'll do it."*

YES-15: *"I also discussed it with her [his sister] but at the time she said something like, 'Yes, if they find using me for that useful', or you know, something similar, I don't remember what she said exactly. But she had no objection whatsoever, so okay."*

Other patients had always had a care-avoiding attitude, leading to an LG's projection of these feelings on trial participation.

NO-05: *"This lady was very care-averse, very suspicious. We managed to get her into a nursing home after a lot of effort, and my guess is that she'll immediately say: 'No, I'm not joining in with that.' I think that's her default position."*

Disease stage. A recurrent but somewhat conflicting factor was the patient's disease stage. Some LGs argued that the advanced condition of the patient motivated them to grasp every chance for improvement. Other interviewees reported that they would have likely been more willing to give consent if the patient had been in better health. The quotes below illustrate that the same advanced disease stage can result in different decisions.

YES-03: *"...he was just very agitated, so we thought, okay, anything that can help, let's give it a go, because he [her father] was so agitated, so maybe...and nothing ventured, nothing gained, that idea."*

NO-10: *"... If she [his mother] had also been in good physical shape... Then I might have said: let's give it a try. Even if it doesn't help, no harm done. But then again: what is the point at this age?"*

Stability. Whereas serious behavioral problems linked to dementia convinced LGs to give consent, a more stable clinical situation was a motivator to avoid potentially disruptive interventions. Especially if the patient was doing quite well compared with his or her co-residents.

NO-02: *"She's [her mother] lived on that ward for over 3 years now and she's still the best of the bunch. Many others have already passed on and new ones have come. We are so pleased with how she is coping there, we don't want anything at all to interfere with it."*

NO-17: *"But I have also seen people there with a very different sort of dementia. And then I think: if someone is aggressive and difficult, then you're more likely to join a study like this just to see if things improve. Do you follow me? If someone is already frustrated or panicky, then I suspect that you're more likely to experiment with medication, to be brutally honest."*

Factors on the level of the proxy

In addition to the study- and patient-related factors, we identified factors connected with the LG him/herself. These interplaying opinions and attitudes of the proxy were crucial for the evaluation of the study- and patient-related factors.

Past experiences. A first factor was the LG's past experiences related to the study or research in general. How those earlier encounters were experienced, played a significant role in the decision-making process.

YES-19: *"We had already spoken to a geriatrician ourselves, actually quite a while ago, who told us that the medicines were causing his [her father] blood pressure to drop way too much. And that that isn't good for someone his age, that they would rather see 120/80. And she [the geriatrician] already concluded then that we should phase out at least one, let's say."*

YES-12*: "I know that before that particular study, there was also another study. I seem to remember that was also called the Danton study, or a variant of it. We also took part in that…and I knew that this is actually a study to see what stopping blood pressure drugs… So yes, we were like, in itself we felt it might also be useful to take part in the study."*

NO-06: *"That [stroke] left her [her mother] depressed and we really felt that nothing more must happen, otherwise she might go completely blind or develop some other medical condition. That's the reason why we're saying that we're not going to mess about with her."*

Altruism and individualism. More intrinsic elements of the LG also influenced the decision process. Some LGs had an altruistic attitude toward science and society, whereas others mainly focused, more individualistically, on the (sensed) missing direct benefit for the patient and/or themselves.

YES-05: *"Not really specifically related to my mother, because I realize perfectly well that this research, scientific research simply takes time, it needs to be placed in a broader context before things can be proven. My mother won't be around forever, what is it going to mean for her? But then I hope that many other people will benefit after she's gone."*

YES-17: *"And I always think it's good to do research into, well, I'd almost say, any major disease, so that in the future we might be able to help other people much better than we can right now."*

NO-15: *"And what's the advantage? For her [her mother-in-law] cognition, for example? How will it help her and us as a family? That's the reason why I thought the study is not much use to her at the moment. That's why I wrote that at the moment it doesn't seem to have any advantages."*

Table 2
Quotes Illustrating the Role of the Other Stakeholders That are Involved in the Process of Proxy Decision-Making on Research Participation of Older NH Residents With Dementia

Stakeholder	Effect	Quotes Illustrating the Influence of the Stakeholder
Other proxies	FACILITATING	**YES-09**: *"It wasn't a spur of the moment thing to think we're doing it. My gut says we should do it, together with permission from other people who endorse what I was thinking."*
		NO-06: *"The 4 of us consult on everything. That does make a difference. I don't have to make the decision alone. Then we arrange things. What would be better? What wouldn't be better? Who feels good about this and who feels good about that? The 4 of us are usually pretty much in agreement about things."*
	IMPEDING	**NO-16:** *"But I am not alone in this, I also have a sister. You need to decide together, and she didn't want us to do it...I thought it might be worth trying, but my sister really didn't want to."*
		NO-12: *"The social dynamic is somewhat more complicated: you aren't deciding things about yourself, you're deciding for a group and that may come with potential feelings of guilt and an uncertain dynamic."*
HCP	REASSURING	**YES-08:** *"Because I was concerned about that part, what if we start to taper off the medication and the blood pressure does increase, what then… It was nice to get an answer from the doctor about that. That was certainly true for me, I wanted that question answered."*
		YES-05: *"For my part there is also a degree of familiarity and trust concerning the residential home or nursing home. I'm not saying I don't have any trust in you [the interviewer/researcher], let me be clear about that. It is simply an issue of unfamiliarity, I think that's where the difference lies."*
	ABSENT	**YES-02:** *"Now look, I have always had a bit more feeling for science than for a general practitioner, because every now and then he comes across as a wretch blundering around in the darkness; I have a bit more confidence in the* ******BLINDED****** *[University Medical Center]."*
		NO-14: *"I actually didn't even think about talking to the care home doctor. To be honest, we haven't got much of a relationship with the doctor. This is not meant as criticism, but the doctors at the care home are constantly changing, so it is very difficult to build a relationship with them."*
		NO-07: *"If my mother's personal physician, one of those new nursing home doctors, had asked me this so that I could immediately ask my own questions, things might have gone very differently. Then I would have understood a lot more of what it was all about."*

Decisional regret. The ability to accept uncertainty related to the study's experimental nature had a major impact on how LGs made the benefit-risk evaluation. Refraining LGs mentioned the uncertainty in research that positive effects outweigh the negative effects. The anticipation of decisional regret and consequential feelings of guilt were described. For some interviewees this decisional regret would be absent if a physician would propose the same intervention in a nonexperimental setting, suggesting a shift in responsibility.

> **YES-17**: *"I just weighed the options and came to the conclusion that I outlined earlier, and yes, of course something could go wrong, but whatever, things can also go wrong when crossing a busy road. So yes, it's all in the game, right?"*
>
> **NO-12**: *"I don't want to be in a situation where something is done accidently, and then something unintended happens to my mother that causes my father to spend the rest of his life saying 'Do you see now? We really shouldn't have messed about with her blood pressure.'"*
>
> **NO-05**: *"Then it's proven, however limited it may be, that it works and that the benefits outweigh the risks. But that's not definite yet. So if she [the doctor] had suggested it as part of treatment or care, I would certainly have gone along. But right now it's really about the experimental character."*

Trust. The fourth and last proxy-related factor that emerged, was the concept of trust. Not only trust in the coordinating research institute but also trust in the local NH staff and health care in general, affected the decision.

> **YES-17**: *"In all fairness, I assume, also given the fact who is doing the research, the institute involved, that they also have a major interest in doing it properly, doing it carefully, et cetera. This isn't some local clinic on the corner, simply said you work for a serious organization."*
>
> **NO-09**: *"Yes, for that matter. I do wonder a little bit whether had she [her mother-in-law] been in a home in which I am actually confident that things are well managed, then I think we might have arrived at a different outcome."*
>
> **YES-05**: *"Actually, I always give the same answer, whether it's the nursing home or doctors: I'm not the expert here. And I take the position: do that which you deem necessary to ensure that my mother can live/function as optimally as possible."*

Other Stakeholders

Most LGs acted in consultation with others. Two other groups of individuals were identified to modulate the process: (1) other proxies and (2) treating health care professionals (HCPs).

Other proxies

Other proxies of the patient, such as siblings, children, and spouses, were asked whether they approved the opinion of the LG. Sometimes consulted family members facilitated the decision by simply confirming the LG's initial preference. Often consent was a result of a joint agreement (see Table 2), whereas for some LGs, other proxies impeded the process. A lack of consensus or complex social dynamics led to a revoked initial consent. These social dynamics were intertwined with the concept of decisional regret.

Health care professional

The second stakeholder who we identified as influencing the final decision, was the HCP responsible for the medical care of the patient. As reported earlier, several LGs discussed study participation with HCPs of the NH, leading to the reassurance of the decision taken (see Table 2). We identified trust in the local HCPs as affecting the final decision. Others did not report any need for the involvement of HCPs. In this context, limited knowledge or frequent staff changes were mentioned. Other LGs mentioned that the HCP had not played any role in the decision process and named opportunities for the physician to act as a bridge between the research institute and the patient's family.

Summarizing Schematic Diagram

After combining all factors on the different levels (study, patient, and proxy) with the influence of other stakeholders (other proxies,

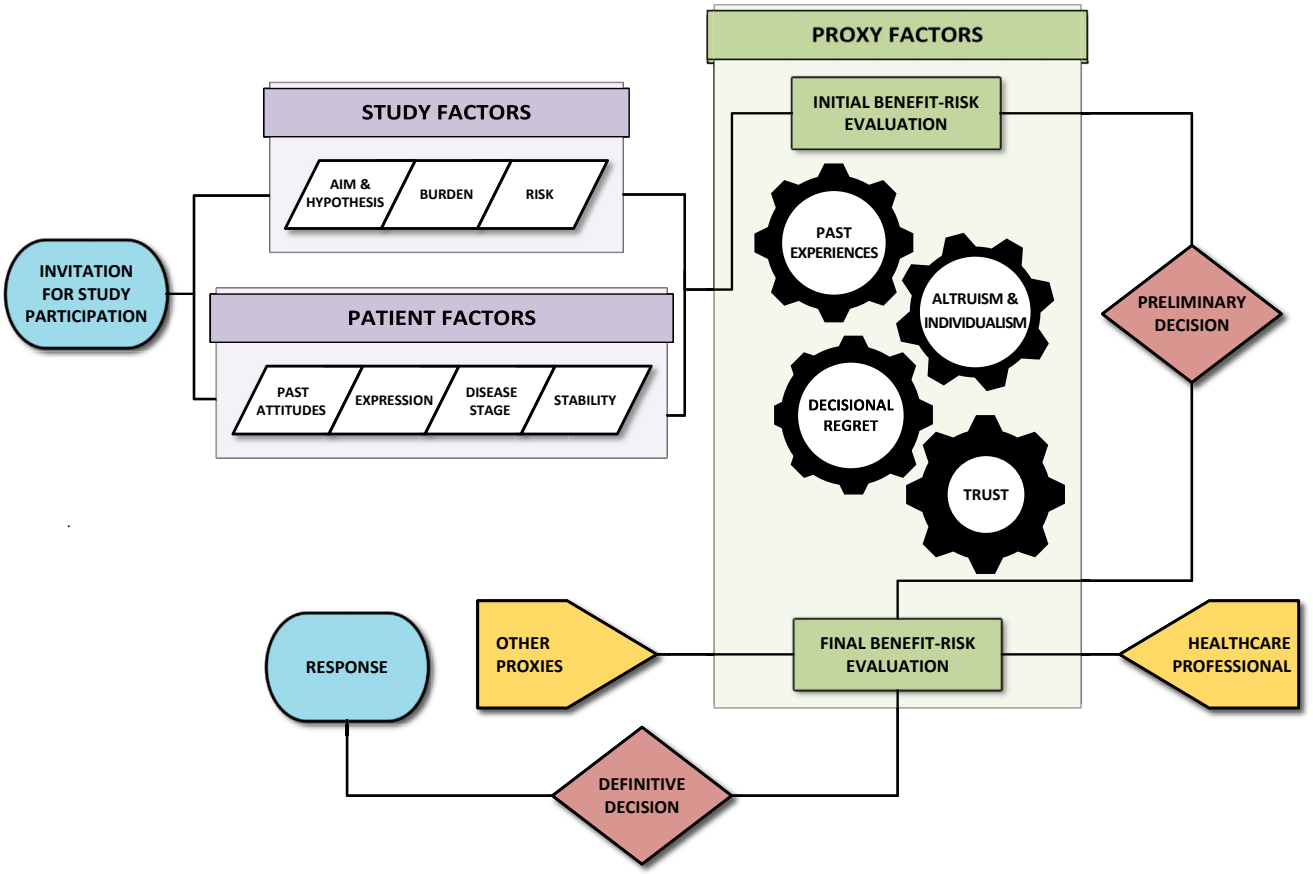

Fig. 1. Schematic diagram describing the process of proxy decision-making on study participation of older adults with dementia. When an LG receives an invitation to give proxy consent for participation in research, factors on the level of the study and patient are weighed, leading to an initial benefit-risk evaluation and a preliminary decision. The mechanism of weighing those study- and patient-related factors is influenced by interplaying opinions and attitudes of the proxy. This initial benefit-risk evaluation is, when necessary or preferred, presented to other relatives of the patient and/or a treating HCP. With the input of these stakeholders, the initial benefit-risk evaluation can be modified, resulting in a final benefit-risk evaluation and a definitive decision.

HCPs) on the final decision, we constructed a step-by-step schematic diagram. Figure 1 describes the process of proxy decision-making in the context of clinical research in older adults with dementia. The moment when an LG is invited to give proxy consent for research, factors on the level of the study and the patient are weighed, leading to an initial benefit-risk evaluation and a preliminary decision. The mechanism of weighing those study- and patient-related factors is influenced by interplaying opinions and attitudes of the proxy. This initial benefit-risk evaluation is when advice or reassurance is needed, presented to other proxies and/or to a treating HCP. With the input of these 2 stakeholders, the initial benefit-risk evaluation can be modulated, resulting in a final benefit-risk evaluation and a definitive decision.

Discussion

In this qualitative analysis of interviews with both LGs who consented to and refrained from giving proxy consent for the participation of an older adult with dementia in a clinical trial, we identified 3 study- and 4 patient-related factors. Guided by interplaying opinions and attitudes, these 7 factors are weighed by the LG in a process that leads to an initial benefit-risk evaluation and corresponding decision. This preliminary decision can be impeded or reassured by additional stakeholders, such as other proxies or a treating HCP, leading to a definitive decision.

This study confirms previously defined aspects affecting proxy decision-making on research, such as the fear of side effects,[13] earlier preferences,[14] and the patient's disease stage.[15] Also more abstract proxy-related factors that we identified, including altruism,[16-19] trust,[17,19] and past experiences[13] accord with prior studies. Although corresponding with existing literature, these factors were to our knowledge not earlier recognized as an interconnected framework leading to an overall (modifiable) benefit-risk evaluation. The present comparison of interviews with both consenting and refraining LGs exposed that the identified factors act as individual scales that can be tipped by the context. Opinions on straightforward aspects of the current intervention, varied not only between but also within LGs, strongly influenced by time-varying factors such as clinical stability, disease stage, and trust in the NH staff. This underlines the finding that the theoretical hierarchy of substituted judgment (what the patient would have decided if capable) above the best interest standard (what is currently the best for the patient) concerning research participation, in reality, overlaps.[20,21] Moreover, in context of research on stopping or not starting a treatment, these concepts do not include anticipation on the decisional regret of changing "a status quo." This principle is earlier reported in the literature on decision-making by HCPs when treating dementia-related behavioral problems[22] and in studies comparing the dementia caregivers' goal of care and their actual decisions regarding life-extending treatments.[23]

Extrapolation of our results has implications for all parties involved. Although valuable tools to aid proxy decision-making in

research have been developed,[24] insights into their own attitudes that direct the weighing of "objective" study- and patient-related factors could help to reassure LGs that their decision is taken to their best knowledge and belief. With these results, researchers could gain insights into the other than study-related concepts that play a role in the decision-making process. The personal context of the patient somewhat conflicts with the standardized RCT setting, but researchers could explicitly state trial-specific possibilities and responsibilities in the accompanying study information. And third, although the consent procedure is primarily an interaction between the dyad of the patient-LG and the researcher, our results show that LGs seek reassurance from HCPs and describe their absence in the process as a missed opportunity. The treating HCP could be the autonomous professional who can apply the RCT's formal and rigid framework to the individual patient context while acknowledging the LG's opinions and attitudes.

The major strength of this study is its direct comparison of interviews with both consenting and refraining LGs in a nontheoretical setting with real-life consequences. The fact that this qualitative analysis was performed, contrary to most previous studies,[20] alongside a nonhypothetical RCT that investigated a tangible research question in the underexposed NH setting, underlines its uniqueness and relevance. Several limitations must be considered when interpreting our results. Because of the COVID-19 pandemic, all interviews took place by telephone, resulting in a loss of human encounter, but giving a fairer opportunity to participate and balance the interviewer-interviewee power relationship.[25] Furthermore, to not jeopardize proxy consent, interviews with consenting LGs took place at the completion of the patient's study period. Therefore, the introduction of recall and outcome bias is plausible. Last, our study took place in Dutch NHs where medical decision-making is coordinated by an elderly care physician.[26] Since these NH-affiliated professionals are specialized in care for frail older adults, our results cannot be extrapolated to all contexts.

Conclusions and Implications

In the proxy decision-making on trial participation of an older adult with dementia, LGs weigh factors related to the study and patient, leading to an initial benefit-risk evaluation and corresponding decision. This preliminary decision is influenced by interplaying opinions and attitudes of the LG and can be modulated by other proxies or an HCP involved in the treatment of the patient, leading to a definitive decision. Although insights into these underlying mechanisms could facilitate the proxy decision-making process for both LGs and researchers, treating HCPs could act as an independent party.

Acknowledgments

The authors thank all legal guardians who were willing to be interviewed, the participating nursing homes, and their elderly care physicians, the mentor organization Haag & Rijn, and the members of the Older Persons Advisory Board Care & Well-being South Holland North, who all facilitated this study.

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Supplementary Table 1
Demographic Characteristics of the Members of the Older Persons Advisory Board Care & Well-being South Holland North Who Participated in the Focus Group Discussions That Formed the Basis of the Interview Guide Used in the Qualitative Analysis

No.	Sex	Age, y	Relation to Older Adult With Dementia
1	Female	63	HCP in an NH, volunteer LG
2	Female	70	Daughter
3	Female	n/a	HCP in an NH
4	Male	76	Brother
5	Male	70	Spouse
6	Male	71	Spouse

n/a, not available.

Supplementary Table 2
Demographic Characteristics of the LGs Who Participated in the Semi-Structured Interviews That Formed the Basis of the Interview Guide Used in the Qualitative Analysis

No.	Sex	Age, y	Relation to Older Adult With Dementia	Recruited via
1	Female	23	Volunteer legal guardian	Professional agency for guardianship (Haag & Rijn)
2	Female	71	Volunteer legal guardian	Professional agency for guardianship (Haag & Rijn)
3	Female	77	Volunteer legal guardian	Professional agency for guardianship (Haag & Rijn)
4	Female	63	Daughter	NH in The Hague-Leiden area
5	Male	70	Spouse	NH in The Hague-Leiden area
6	Female	40	Daughter	NH in The Hague-Leiden area

Supplementary Table 3
Interview Guide That Was Used in the Interviews With LGs Who Consented to Trial Participation of Their Relative/Ward With Dementia

Questions regarding the decision process
- You have given proxy consent for your relative to participate in the ***BLINDED*** study.

How did that decision process go?
- What were the most important considerations for you to give proxy consent?

And are these considerations specific to this study?
- Have you ever been asked before to give proxy consent for your relative in the context of research?
  - If yes: what were the reasons why you did (not) give proxy consent for that study?
  - If applicable: why was your decision for this study different?

Questions regarding experiences and opinions about deciding for yourself in the context of research
- Have you ever been asked to participate in research?

What were the reasons to consent to/refrain from participation?
- You have given proxy consent for the participation of your relative in the ***BLINDED*** study.

What is it like to make such a decision in comparison with deciding for yourself? (You can give a hypothetical answer if you have never been asked to participate in research.)

Role of the treating physician
- What role did the primary physician of your relative play in the decision to give proxy consent?
- Suppose the primary physician of your relative suggested reducing (some of) your relative's prescribed antihypertensive drugs, on his/her own initiative and outside of a scientific context, how would you have looked at the proposition in that situation?

Signing the informed consent form and insurance documentation
- How did you experience giving proxy consent for study participation using a signature?

How does this compare with giving verbal proxy consent, for example for the start of a new drug in the context of regular care?
- The study information was accompanied by an insurance document. What did you think about this information? How did this information play a role in the decision process?

Perspectives and attitudes on research in the past
- Can you tell me about conversations, now or in the past, you may have had with your relative about participating in scientific research or about scientific research in general?

Supplementary Table 4
Interview Guide That Was Used in the Interviews With LGs Who Refrained From Giving Proxy Consent for Trial Participation of Their Relative/Ward With Dementia

Questions regarding the decision process
- You have *not* given proxy consent for your relative to participate in the ***BLINDED*** study.

How did that decision process go?
- What were the most important considerations for you to *refrain from* giving proxy consent?

And are these considerations specific to this study?
- Have you ever been asked before to give proxy consent for your relative in the context of research?
  - If yes: what were the reasons why you did (not) give proxy consent for that study?
  - If applicable: why was your decision for this study different?

Questions regarding experiences and opinions about deciding for yourself in the context of research
- Have you ever been asked to participate in research?

What were the reasons to consent/refrain from participation?
- You have *not* given proxy consent for the participation of your relative in the ***BLINDED*** study.

What is it like to make such a decision in comparison to deciding for yourself? (You can give a hypothetical answer if you have never been asked to participate in research.)

Role of the treating physician
- What role did the primary physician of your relative play in the decision to *refrain from* giving proxy consent?
- Suppose the primary physician of your relative suggested reducing (some of) your relative's prescribed antihypertensive drugs, on his/her own initiative and outside of a scientific context, how would you have looked at the proposition in that situation?

Signing the informed consent form and insurance documentation
- In the ***BLINDED*** study, you were invited to give proxy consent for study participation by using a signature. How does this compare with giving verbal proxy consent, for example for the start of a new drug in the context of regular care?
- The study information was accompanied by an insurance document. What did you think about this information? How did this information play a role in the decision process?

Perspectives and attitudes on research in the past
- Can you tell me about conversations, now or in the past, you may have had with your relative about participating in scientific research or about scientific research in general?