Older persons' and their caregivers' perspectives and experiences of research participation with impaired decision-making capacity: a scoping review

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Conflicts of Interest

None to declare.

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ABSTRACT

Background and objectives

Human research ethics statements support equitable inclusion of diverse groups. Yet older people are under-represented in clinical research, especially those with impaired decision-making capacity. The aim of this study was to identify perspectives and experiences of older persons and their caregivers of research participation with impaired decision-making capacity.

Research design and methods

Scoping review of literature and online sources in January-February 2019 (updated June 2020) according to Joanna Briggs Institute methodology and PRISMA Extension for Scoping Reviews. English-language peer-reviewed research articles and Australian online narratives were included. Data were tabulated and narratively synthesized.

Results

From 4171 database records and 93 online resources, 22 articles (2000-2019, 82% United States, 16 first authors) and one YouTube webinar (2018) were initially included; updated searches yielded an additional article (2020) and YouTube webinar (2020). Studies were heterogeneous in terminology, methods and foci, with hypothetical scenarios, quantitative analyses and examination of proxy consent predominating. Participants (n=7331) were older persons (71%), caregivers of older persons with dementia/cognitive impairment (23%) and older persons with dementia/cognitive impairment (6%). Synthesis identified two themes: willingness to participate and decision-making approaches.

Discussion and implications

Research participation by older persons with dementia may be optimized through reducing risks and burdens and increasing benefits for participants, greater consumer input into study development, and shared and supported decision-making. Older persons' and caregivers' perspectives and experiences of research participation with impaired decision-making capacity require investigation in a greater range of countries and conditions other than dementia, and dissemination through more varied media.

Key words

Decision Making, Ethics (research, practice, policy, individual choices), Analysis – Scoping Review

Background and objectives

Research seeking to improve health, function and quality of life requires representative samples. Yet older persons are under-represented in research relevant to their needs, especially those with impaired decision-making capacity (Ridda, MacIntyre, Lindley, & Tan, 2010). Research exclusion of this group of older persons impairs external validity of many clinical studies, reducing opportunities to equitably build evidence for the benefits and harms of healthcare interventions (Ries, Thompson, & Lowe, 2017).

This selection bias is multi-factorial. Informed consent and valid outcome measurement are more challenging when cognitive or communication impairments are present (Ridda et al., 2010). Researchers may lack pre-requisites to tailor methods and measures and instead use exclusion criteria to circumvent the challenges. Older people are often stigmatized, even more so when cognitive impairment is present (Evans, 2018), or considered too vulnerable for research participation (Bracken-Roche, Bell, Macdonald, & Racine, 2017). When proxy consent is used, proxy decision-makers (i.e. the person permitted by law to make decisions on behalf of another) may be uncertain of or disagree with the other's preferences (Reamy, Kim, Zarit, & Whitlatch, 2013). International and national human research guidance supports equitable inclusion of diverse groups, yet varies in explanation and categorization of relevant ethical principles and processes (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada, 2014; Dobson, 2008; "International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition," 2016; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978; The National Health and Medical Research Council, Australian Research Council, & Universities Australia, 2007 (Updated 2018)). Jurisdictional statutes and research ethics committees use different terms, definitions, degrees of inclusiveness and permissible consent processes, with some more restrictive than the overarching guidance (Ries et al., 2017). Individual reviewers, researchers, ethics committee members and clinicians also vary in attitudes, knowledge and practice regarding research inclusion of people with impaired decision-making capacity (Prusaczyk, Cherney, Carpenter, & DuBois, 2017; Ridda et al., 2010).

Given this complex landscape, the aim of this study was to identify what is known about older persons' and their caregivers' perspectives and experiences of research participation for those with impaired decision-making capacity. The primary objective was to review relevant international peer-reviewed research literature on the topic. To inform future local initiatives to improve research participation by older people with conditions impacting decisional capacity, the second objective was to review relevant online contemporary accounts by older Australians.

Methods

A scoping review of published literature and online sources, according to Joanna Briggs Institute methodology (The Joanna Briggs Institute) and PRISMA Extension for Scoping Reviews (PRISMA-ScR). (Tricco et al., 2018).

Search strategy

We performed a database search of international literature in January 2019 in Medline, CINAHL, Cochrane, EMBASE, Web of Science and PsycInfo, using relevant terms for the participants (older people and caregivers) and concepts of interest (conditions affecting cognition; research participation; perspectives and experiences), with a lateral search of references of identified relevant articles. In February 2019, we searched websites of 30 pertinent Australian health advocacy organisations (nominated by investigators) for relevant narratives. Lastly, a Google search on February 11, 2019 for additional relevant webpages with eligible narratives, with the limit set to Australia and browsing history cleared before each new search. Reviewers appraised Web pages of each Google search against eligibility criteria and followed potentially relevant links until 10 consecutive ineligible ones were found. YouTube video lists were systematically scrolled, potentially eligible videos identified and further relevant links pursued, for a maximum of one hour per search term (Luckett et al., 2016). All searches were repeated in June 2020.

Full details of the search terms and websites are reported in Supplementary file 1.

Selection criteria

Included data sources were: i) research articles reporting perspectives and/or experiences of older persons (including those with and without cognitive impairment) and their caregivers of participating in research with impaired decision-making capacity, published in international English-language peer-reviewed journals with no date limitations; and ii) relevant online narratives (e.g. blogs, chats and/or commentaries, spoken or written) by older persons or their caregivers on Australian websites. Sources primarily reporting professional advocates', health carers' or researchers' perspectives of the topic, or not reporting a majority (i.e. <50%) of older participants and/or caregivers or age of the sample, were excluded.

Data charting and synthesis

Database search results were imported into Endnote X7 then Covidence (www.covidence.org, Veritas Health Innovation Ltd.) One reviewer [AG] applied eligibility criteria to all titles and abstracts with others performing the second independent screen [AH, SK, CS, AC, IAD, LX]. Two reviewers [AH, SK, IAD, LE] independently appraised each full text, compared decisions and resolved discrepancies

through discussion [AH, LE, SK, CS, AG]. LE extracted data relevant to study authors, country of origin, aims, design, sample, methods and results into an Excel V15.28 spreadsheet, AH undertook independent checking, and discrepancies were resolved by discussion [LE, AH, SK].

Four reviewers [AG, AH, AC, MV] extracted online narrative data relevant to the organisation, URL, focal health condition, target audience, country, date, type of commentary and its URL, title, author and content into a second Excel V15.28 spreadsheet.

LE, AH and SK presented extracted and tabulated data to the full investigator team, consumers (i.e. people with lived experience of relevant health issues) (NHMRC, 2018) and researchers with topic expertise in a face-to-face/Zoom workshop in October 2019 to obtain ranging perspectives in interpretation. Of note, while no consumer who contributed to the study as an investigator [IG] or workshop participant had a condition that impaired their decision-making capacity, all were aged over 65 years and had experience of serious or chronic illness and/or caring for a family member with dementia or other life-limiting conditions.

Ultimate reporting of results was via summation of source and participant characteristics, summary tables, and narrative synthesis of all findings (Popay et al., 2006), using source terminologies and rounding of quantitative results to whole numbers.

In keeping with scoping review methodology, we did not assess included studies for risk of bias (The Joanna Briggs Institute; Tricco et al., 2018).

Results

From 4171 identified database records, we initially included 22 research articles by 16 first authors. Four first authors contributed to eleven articles (50%), one to seven (32%) and another was an investigator of this review [NR]. The first search of Australian websites identified 93 potentially relevant online resources, of which we included one: a 2018 YouTube webinar on dementia research Updated searches in June 2020 yielded one additional article (2020) and another YouTube webinar (2020). Overall, 23 research articles and two online sources were included (Figure 1).

Characteristics of included sources

Research articles

Studies were conducted in the United States (US) (n=19), Canada (n=2), Australia (n=1) and Israel (n=1), published during 2000-2020. Sixteen (70%) included caregivers, 14 (61%) included participants experienced in proxy decision-making for an older person with dementia and nine (39%) included participants with dementia and/or cognitive impairment.

Of 7331 total participants, 5189 (71%) were older persons with no diagnostic information reported (mean age 76); 1685 (23%) caregivers of older persons with dementia/cognitive impairment (mean age 63); and 457 (6%) older persons with dementia/cognitive impairment (mean age 76). Dementia/cognitive impairment was variously ascertained and ranged in severity from mild to severe. Terminology for participants varied, with some articles using terms for persons with dementia that were seemingly contrary to more recent recommendations for "accurate, respectful, inclusive, empowering and non-stigmatizing" language ("Dementia Language Guidelines," 2018); for example, "demented patients" and "noncompetent" (Table 1).

Studies were also heterogeneous in methodology and foci. Methods included:

1. Structured interviews/questionnaires (n=11, 50%), with 1634 participants overall (901 older adults [262 with dementia or cognitive impairment] and 733 caregivers; mean sample 149 [range 29-538]. Eight of these studies used structured tools to measure participants' understanding, attitudes, illness severity and/or function (Table 2). All 11 were quantitative, with two incorporating qualitative analyses.
2. Surveys (n=8, 36%), with 5486 participants overall (818 caregivers, 229 older persons at risk of dementia and 141 older persons with cognitive impairment; mean sample 686 [range 67-1515]).
3. Focus groups (n=2, 9%), with a combined total of 80 caregiver participants; mean sample 40 [range 30-50]).
4. Semi-structured interviews (n=2, 9%) with a total of 54 persons with dementia/cognitive impairment, 54 caregivers and 23 other older persons; mean sample 66 [range 33-98]

Overall, fifteen articles (68%) reported perspectives of older persons towards consent and/or participation in hypothetical research with varying risk/burden and benefit, including trials of drugs, exercise and other interventions to treat dementia, genetic studies and brain donation after death. Ten studies (43%) were situated within 'parent' studies, mostly drug trials and population-based surveys.

A summary of the included studies is presented in Supplementary file 2.

Online sources

The two online sources were webinar discussions. The first included a woman with Alzheimer's disease, her husband and carer, researchers, clinicians and pharmaceutical industry persons (total n=7), entitled "Let's Talk Dementia Research Webinar 1: Demystifying Trials, Access and Understanding" (Alzheimer's Disease International, 2018). The second, "Consumer perspectives in

dementia research" included a woman with frontotemporal dementia, a man with Lewy Body dementia, and the wife of a man with Alzheimer's disease, along with three dementia researchers (total n=6) (NHMRC National Institute for Dementia Research, 2020).

Narrative synthesis

Synthesis of findings across sources is presented as two themes: willingness to participate and decision-making approaches.

Willingness to participate

Varying majorities were willing to support, participate, enrol another and/or agree to dementia-related research with impaired decision-making capacity, and for consent to be provided by a proxy (most often a family member) (Ayalon, 2009; Bardach, Parsons, Gibson, & Jicha, 2020; Bravo, Paquet, & Dubois, 2003; Calamia, Bernstein, & Keller, 2016; Kim et al., 2009; Kim, Kim, McCallum, & Tariot, 2005; Ries, Mansfield, & Sanson-Fisher, 2019). Willingness to participate was positively associated with lower study risks and burdens (including less travel to study centers), perceived potential for benefit (direct and indirect), and positive research attitudes (Ayalon, 2009; Bardach et al., 2020; Bravo et al., 2003; Calamia et al., 2016; Dunn, Hoop, Misra, Fisher, & Roberts, 2011; Jefferson et al., 2011; Karlawish, Cary, Rubright, & Tenhave, 2008; Karlawish et al., 2009; Kim et al., 2009; Kim et al., 2005; Ries et al., 2019). Feeling valued, more closely monitored, supported and/or mentally stimulated by the research team/process were reported as motivators or re-enforcers in all of the four qualitative studies (Austrom et al., 2011; Bardach et al., 2020; Connell, Shaw, Holmes, & Foster, 2001; Sugarman, Cain, Wallace, & Welsh-Bohmer, 2001); with one further reporting that participants valued the "positive and enjoyable" environment of the research center (Bardach et al., 2020).

Positive research attitudes almost always overcame the effect of other individual variables; including minority ethnicity of US participants (Ayalon, 2009; Kim et al., 2009; Kim et al., 2005), which without multivariate analyses was a significant variable or thought to require a tailored approach to recruitment (Connell et al., 2001; Jefferson et al., 2011; Stocking et al., 2006). Common motivations to participate were altruism, potential benefit for the person with dementia, and improved scientific knowledge (Alzheimer's Disease International, 2018; Austrom et al., 2011; Bardach et al., 2020; Bravo et al., 2013; Bravo et al., 2003; Calamia et al., 2016; Connell et al., 2001; Dunn et al., 2011; Jefferson et al., 2011; Ries et al., 2019; Sugarman et al., 2001). A greater range of influential circumstantial and relational factors was reported when decision-making was actual rather than hypothetical (Black, Wechsler, & Fogarty, 2013; Elad et al., 2000; Karlawish, Casarett, & James, 2002; Kim et al., 2009). Hope, desperation with regard to cure, and lack of other options also influenced

decisions (Alzheimer's Disease International, 2018; Bardach et al., 2020; Elad et al., 2000; Sugarman et al., 2001).

The online narratives by persons actively involved in dementia research (Alzheimer's Disease International, 2018; NHMRC National Institute for Dementia Research, 2020) revealed their willingness to participate was motivated by family history and legacy; hope; direct (e.g. improved physical and cognitive abilities during and after participating in a study of high intensity weight training: "*One of the best things that has happened to me, by the way*") and indirect benefits (e.g. increased networks and opportunities to advocate for people with dementia); contributing to knowledge; and addressing unmet needs for people with dementia. For example:

> "*Hope was important as I was concerned for my sons and grandchildren and future generations, especially since I had a genetic link. I also saw it as a worthwhile exercise as I had an interest in research methods*."

One woman described how she became involved in research because she was mindful of her potential future experiences in residential aged care. Another stated she did so after her husband, a retired surgeon with Alzheimer's disease, requested that she take him home so that he could resume watching a Stephen Hawking's series about the universe instead of an organised activity that involved rolling balls down a slope. Two other narrators highlighted that many people with dementia require more than "*balloon games and bingo*" to maintain their abilities and quality of life. With regard to advocacy for others, one man recounted how his involvement in research led him to state in a presentation to a large group of stakeholders, "*We have to remember that this is all about me, and 459,000 people living with dementia in Australia*".

The narrators' willingness to participate in research appeared resilient and yet, as in the included studies, was not absolute, as some outlined how researchers could improve the experience of participation by persons with dementia and their caregivers. They recommended using respectful language (with one narrator explicitly referring to an Australian guideline) ("Dementia Language Guidelines," 2018); person-centeredness; adopting a fighting rather than nihilistic attitude towards dementia; actively collaborating with people living with dementia in all stages of the study process; and providing appropriate information and support throughout studies, including at cessation (Alzheimer's Disease International, 2018; NHMRC National Institute for Dementia Research, 2020).

Decision-making approaches

While proxy research consent was the predominant focus, decision-making was also found to be highly diverse and multi-factorial (Black et al., 2013; Elad et al., 2000; Karlawish et al., 2002; Karlawish, Kim, et al., 2008; Stocking et al., 2006). It generally involved discussions between many

persons, including the person with dementia, their proxy, other family members, clinicians and researchers, and it was not always clear who made (or should make) the ultimate decision (Austrom et al., 2011; Sugarman et al., 2001). There was imperfect congruence between older persons' and proxies' choices, with rates of agreement higher for those with supportive relationships and prior communication about research preferences (Black et al., 2013; Karlawish et al., 2002; Karlawish, Kim, et al., 2008). Hypothetical advance research directives were of interest to two cohorts, especially for lower risk studies (Karlawish et al., 2009; Ries et al., 2019). However, elsewhere advance documented preferences were also found no more congruent with current preferences than with surrogate predictions (Herault, Bravo, & Trottier, 2018).

Informal caregivers who made health-care decisions for an older person with dementia were commonly the presumed (Ayalon, 2009; Kim et al., 2009) or preferred (Bravo et al., 2003; Ries et al., 2019) future research proxies. Five studies reported participants gave proxies complete or partial leeway to override their current stated preferences in the future (Ayalon, 2009; Bravo et al., 2003; Karlawish et al., 2009; Kim et al., 2009; Stocking et al., 2006). Being willing to participate in research was positively associated with willingness to give proxies this future leeway (Ayalon, 2009; Bravo et al., 2003; Kim et al., 2009). Another four studies examined ethical standards guiding decision-making, including best interests (seeking to maximise a person's current well-being) and substituted judgement (making a decision that reflects what the person would choose if able to do so) (Dunn et al., 2013; Dunn et al., 2011; Karlawish, Kim, et al., 2008; Stocking et al., 2006). In these studies, more participants endorsed best interests, or best interest combined with substituted judgement, than substituted judgement alone. Proxies considered both past and present wishes of the person with dementia, often integrated best interests and substitute judgment considerations, and frequently prioritised what they thought matched the person's current preferences and tolerances. Proxy decision-making operated and impacted upon spouses differently to children of older people with dementia (Bravo et al., 2013; Cary, Rubright, Grill, & Karlawish, 2015; Elad et al., 2000; Karlawish et al., 2009; Kim et al., 2009), and for those making decisions for persons with earlier stage dementia compared to later (Austrom et al., 2011; Sugarman et al., 2001).

Discussion

This scoping review identified that older persons' and caregivers' perspectives and experiences of research participation with impaired decision-making capacity have been predominantly studied in the US by a discrete group of researchers, focused on investigating dementia pathophysiology, prevention and cure and proxy decision-making via hypothetical scenarios and quantitative methods. Most of the overall sample were not reported to have impaired decision-making capacity,

and an extensive online search of relevant Australian websites contained only two sources containing consumer perspectives on the topic. With these caveats, key findings were as follows. Most, but not all, persons in the included studies supported research participation with impaired decision-making capacity, especially if the study presented lower risk/burden and greater reward and if they themselves had a positive attitude to research. Preferences and decision-making were highly diverse, fluid and circumstantial. Proxy decision-making was often informally shared, and proxies sought to integrate best interests and substitute judgement considerations. Altruistic motivations by older people and proxies to advance knowledge, care, support and advocacy with regards to neurocognitive disorders suggested that affinity with a 'community of illness' (Barnbaum, 2019) was another consideration in their research decision-making. The Australian online narratives by persons with dementia and their spouses added contemporary local perspectives that were congruent with findings of the included studies, as well as lending support to other calls to increase the involvement of persons living with dementia in research design, nomenclature and process (Bethell et al., 2018; "Dementia Language Guidelines," 2018). In the context of dementia, a progressive, life-limiting condition with no effective curative treatment, the finding that desperation also influenced decision-making about research participation further highlights the need for consumer contribution to study design and process, as well as circumspect presentation of potential benefits to prospective participants.

Overall, factors influencing willingness to participate in clinical research were similar to studies pertaining to other life-limiting illnesses. A qualitative meta-synthesis of what influenced cancer patients to participate in drug trials reported similar factors: trust in physicians, attitudes of and consequences for family, hope of benefit, altruism, cost-benefit considerations, availability of other options, attitudes towards living with cancer and as a way of coping with its psychological impacts (Nielsen & Berthelsen, 2019). A systematic review of perceptions of people receiving palliative care of research participation reported motivations were potential for personal benefit, altruism and desire to retain autonomy, and preferences were for lower risk and burden studies (White & Hardy, 2010). Most recently, a 2019 international survey of 12,451 respondents (26% aged 65 or older) reported motivations to participate in clinical research were to help advance science and treatments and others with the disease, obtain better treatment or treatment education, and receive money; with older respondents more motivated by advancing science and helping others ("Perceptions and Insights Study: Deciding to participate," 2019). The commonality of findings about altruism, desire to contribute to knowledge, hope for benefit, and preference for safe and feasible studies is congruent with key human research advocacy for ethical inclusion of groups of persons who potentially are at increased risk of harm (Canadian Institutes of Health Research et al., 2014; Dobson, 2008;

"International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition," 2016; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978; The National Health and Medical Research Council et al., 2007 (Updated 2018)).

Relevant to findings on approaches to consent for research participation is the movement from *proxy* decision-making to *shared* and *supported* decision-making approaches for people with disability (Australian Law Reform Commission, 2014; Sinclair, Field, & Blake, 2018). Shared decision-making refers to the joint involvement of the person concerned and others involved in their life to reflect, respect and accommodate that person's preferences, priorities and goals (Bunn et al., 2018). This includes situations where the person may require additional means to support their decision-making. Shared decision-making incorporates the provision of evidence-based information, including via decision aids, with personal interaction and continuity of relationship (Bunn et al., 2018). In this approach, the question of who actually makes the decision is secondary to key persons engaging in the process together. In the clinical context, shared decision-making has resulted in better care and outcomes, including greater satisfaction and less conflict (Stacey et al., 2017). Development and testing of shared decision-making as an explicit research consent approach for older persons with impaired decision-making holds potential for better tailoring of information, consideration of the person's preferences and values, reduction of decision-making burden on proxies, and guidance for researchers (Bunn et al., 2018; Clayman, Kumar, Murray, Mok, & Sharpe, 2019).

A distinction of supported decision-making is that it privileges the person with disability as the decision-maker (Sinclair et al., 2018). This approach arose in Canada in the 1990s and has gained prominence in the context of the 2006 United Nations (UN) Convention on the Rights of Persons with Disabilities, which asserts that people with a disability can be enabled to make and communicate decisions affecting their lives (Sinclair et al., 2018). Recommendations of the Convention have been ratified and variously implemented by most UN Member States (Department of Economic and Social Affairs Division for Inclusive Social Development, n.d.). For example, in 2014 the Australian Law Reform Commission (ALRC) developed National Decision-Making Principles to inform Commonwealth, state and territory laws and frameworks relevant to legal capacity (Australian Law Reform Commission, 2014). These are, in brief: equal right to decision-making and respect; obligation to provide necessary support for decision-making; person's will, preferences and rights must direct decisions; and need for legal safeguards to prevent abuse and undue influence (Australian Law Reform Commission, 2014; Sinclair et al., 2018). No studies in the present review focused on supported decision-making. The absence of any findings regarding preferences for supported decision-making in research participation in this review may reflect the fact that this approach is relatively new, and has only recently begun to be explored in the context of people with

age-related cognitive impairments. We suggest that further research should more directly explore the potential role of supported decision-making in the process of consent for research participation (Haberstroh, Oswald, & Pantel, 2017).

The ALRC considers decision-making solely by a proxy as last resort and proxy decisions should, to the extent possible, reflect the will and preferences of the person with disability (Australian Law Reform Commission, 2014; Sinclair et al., 2018). Current research guidance establishes various standards for proxies, referring to decisions that are in, or not contrary to, the person's best interests (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978), substitute judgment (Canadian Institutes of Health Research et al., 2014; Dobson, 2008; "International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition," 2016), or an integrated approach. An example of the latter is within the Australian National Statement on Ethical Conduct in Human Research, which states a person with cognitive impairment, intellectual disability or mental illness unable to provide consent should have their wishes followed: *"…unless changed circumstances mean that acting in accordance with those wishes would be contrary to the participant's best interests*." (The National Health and Medical Research Council et al., 2007 (Updated 2018)).

Findings of this review indicate that participants positioned respecting previous preferences of the older person with dementia as simply one or even a subordinate consideration among many others when actually making a research decision. This highlights how proxies' likely intimate knowledge of the person uniquely positions them to communicate present wishes when that person can no longer do so independently. It also raises the question whether it is reasonable to expect proxies to make decisions based on a person's prior expressed wishes without being influenced by actual research risks, burdens and benefits (for both the person and themselves), as the details and implications of the study under consideration would not have been known when the wishes were previously expressed. This finding also reflects the wider understanding of advance care planning as primarily "*an ongoing process of reflection and communication with key others"*, rather than a static directive (Ries, Mansfield, & Sanson-Fisher, 2020).

Advance planning for research participation is yet to be fully implemented into practice. Of note, no standard advanced research directive (ARD) template or process currently exists. There is also evidence of researchers' uncertainty and inexperience in aligning a person's previously expressed research preferences, current wishes and circumstances, and proxy decision-making. For example, a recent survey of dementia researchers' views on ARDs found that while the majority supported their use and almost all agreed that later dissent by the person overrode prior stated wishes, very few had actually used an ARD, and there was equipoise as to whether prior documented preferences could

be overridden by proxies. These researchers also expressed uncertainty about whether ethics committees/institutional review boards (IRBs) would accept an ARD as a valid expression of a person's willingness to participate in research; and, conversely, some feared IRBs making them mandatory (Ries et al., 2020). Development of evidence, standards and practice for advance research decision-making is therefore required to inform IRBs, research teams and their interactions to best operationalize the practice. In these translation endeavors, older persons' frequent prioritization of current preferences, circumstances and willingness to grant their proxies leeway will be important to consider. Where persons do not have anyone available or willing to be their proxy, ARDs, to the extent that these may be acceptable evidence of willingness to participate (e.g. for low risk activities), may help to overcome this particular barrier to research participation during decisional incapacity.

Limitations

Inclusion of only English-language research articles and Australian online narratives limits findings to high-income countries, particularly the US, which is a significant limitation given the majority of people with dementia live in lower and middle income countries (Prince et al., 2013). Risk of bias of included studies was not assessed, precluding systematic critique of overall strength of evidence. An inherent selection bias is possible due to sources representing mainly white persons, and likely those with more positive research attitudes (Hughes, Varma, Pettigrew, & Albert, 2015). Findings may not be generalizable to older people with non-dementia-related causes of impaired decision-making capacity, such as delirium or coma, or studies of other conditions.

Conclusion

This scoping review of international research literature and Australian online resources to identify older persons' and caregivers' perspectives and experiences of research participation with impaired decision-making capacity included 23 methodologically heterogeneous studies and two sources of online narratives. Predominant foci of included sources were dementia, proxy decision-making, hypothetical scenarios and quantitative methods. Findings highlight that research participation by older persons with dementia may be optimized through reducing risks and burdens and increasing benefits for participants, greater consumer input into study development, and investigation of shared and supported decision-making approaches. Older persons' and caregivers' perspectives and experiences of research participation with impaired decision-making capacity requires empirical investigation in a greater range of countries and conditions other than dementia, and dissemination through more varied media.

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Table 1: Terms used for participants in included articles

Participants	Terms
Older persons with no diagnostic information reported	Older adults/older people/older Americans (n=7)
Persons with dementia/cognitive impairment	Older adults/persons/relatives*/family members* (with condition of interest) (n=7)
	Patients with (condition of interest) (n=5)
	Subjects (n=4)
	Decisionally incapacitated close relatives* (n=1)
	Noncompetent (n=1)
	Demented patients (n=1)
Decision-makers for older persons with dementia/cognitive impairment	Caregivers (n=7)
	Relatives (n=7)
	Proxies (n=6)
	Surrogates (n=5)
	Family members (n=4)
	Carers (n=1)
	Substitute health-care decision-makers (n=1)
	Legal guardians (n=1)

* of the caregiver/proxy participant

Table 2: Structured measures used in included studies

Structured measures	Included studies
Understanding of proposed study	
MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR)	Dunn et al., 2013; Dunn et al., 2011; Karlawish et al. 2008; Karlawish, Kim, et al., 2008; Karlawish et al., 2002; Karlawish et al., 2009
Attitudes	
Research Attitudes Questionnaire (RAQ)*	Cary et al., 2015; Karlawish et al., 2009
Social Responsibility Scale (SRS)	Karlawish et al., 2009
Health Care System Distrust Scale (HCSDC)	Karlawish et al., 2009
Intrinsic Religiousness Motivation Scale (IRMS)	Karlawish et al., 2009
Perceived Threat of Alzheimer's Disease Scale (PTADS)	Karlawish et al., 2009
Function	
Activities of daily living (ADLs)	Cary et al., 2015; Karlawish et al., 2008
Instrumental Activities of Daily Living (IADLs)	Karlawish et al., 2008
Folstein Mini-mental State Examination (MMSE)	Black et al., 2013
Neuropsychiatric aspects	
Neuropsychiatric Inventory Severity subscale (NIS)	Cary et al., 2015; Karlawish, Cary, et al., 2008
Neuropsychiatric Inventory Distress subscale (NID)	Karlawish, et al., 2008

* Original RAQ was developed by Kim, and with further psychometric testing by Kim and two other first authors of included articles, Cary and Karlawish, subsequent to included studies *(Rubright, Cary, Karlawish, & Kim, 2011).*

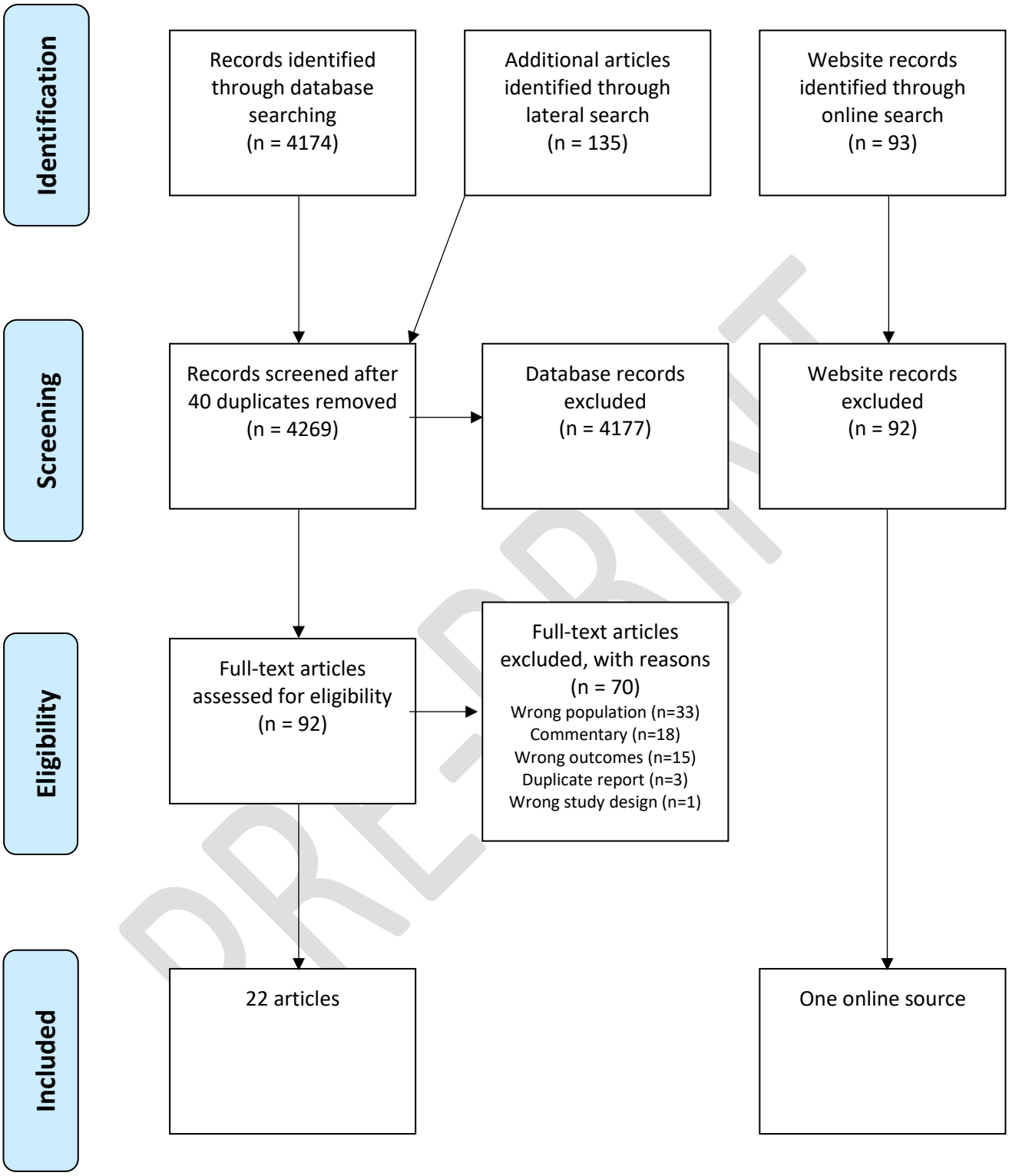

Figure 1: Flow chart of initial searches and inclusion Jan-Feb 2019
Note: The updated searches in June 2020 yielded one additional article and one additional online source

Supplementary file 1: Search terms and websites

Database searches	
Participants/Concepts	**Search terms**
Older people	Humans/ AND Aged/ OR aged.tw. OR geriatric*.tw. OR older*.tw. OR elder*.tw. OR Frail Elderly/ OR Aged, 80 and over/
Caregivers	Humans/(MESH) AND Family/ (MESH) OR Caregiver/ (MESH) OR "carer" OR Legal guardians/ (MESH)
Conditions affecting cognition	Cognition*/ (MESH) OR Cognitive dysfunction/ (MESH) OR Dementia/ (MESH) or Frontotemporal dementia/ (MESH) OR "dementia vascular" OR Dementia Multi-infarct/ (MESH) OR Lewy body disease/ (MESH) or "dementia Senile" OR "dementia presenile" OR Delirium/ (MESH) OR deliri*" OR neurocognitive disorders" (MESH) OR "cognition disorders" (MESH) OR "Intellectual Disability" (MESH) OR "mental disorders"
Clinical research participation	Patient participation/ (MESH) OR Patient selection/ (MESH) OR Research ethics/ (MESH) OR Informed consent/ (MESH) OR "inclusion in clinical trials" OR Decision making/ (MESH) OR "patient activation" OR "patient empowerment" OR "patient involvement" OR "patient engagement" OR "shared decision making" OR "supported decision making" OR "supportive decision making" OR "participatory research" OR "process consent" OR "advanced research directive" OR "patient public involvement"
Perspectives and experiences	Health Knowledge, Attitudes, Practice/ (MESH) or Attitude*/ (MESH) or "views" or "perspectives" or "values" or "beliefs" or Qualitative research/ (MESH) or Focus groups/ (MESH) or Surveys and questionnaires/ (MESH) or "consumer"
Website searches	
Organization	**Website**
ACT Public Trustee & Guardian	https://www.ptg.act.gov.au/
Australian Clinical Trials Alliance	https://clinicaltrialsalliance.org.au/
Brain Tumour Alliance Australia	https://btaa.org.au/
Cancer Australia (and 14 supported Cancer Cooperative Trials Groups)	https://canceraustralia.gov.au/
Cancer Council Australia	https://www.cancer.org.au/
Cancer Voices Australia	https://www.cancervoicesaustralia.org/
Capacity Australia	https://capacityaustralia.org.au/
CareSearch	https://www.caresearch.com.au/Caresearch/Default.aspx
Clinical Oncology Society of Australia	https://www.cosa.org.au/
Cognitive Decline Partnership Centre Supported Decision-Making	https://cdpc.sydney.edu.au/research/planning-decision-making-and-risk/supported-decision-making/
Consumers Health Forum of Australia	https://chf.org.au/
Dementia Australia	https://www.dementia.org.au/
Dementia Friendly Communities	https://www.dementiafriendly.org.au/
Office of the Public Advocate (ACT)	https://hrc.act.gov.au/public-advocate/
Office of the Public Guardian (NT)	http://publicguardian.nt.gov.au/
Office of the Public Advocate (QLD)	https://www.justice.qld.gov.au/public-advocate
Office of the Public Guardian (QLD)	https://www.publicguardian.qld.gov.au/
Office of the Public Advocate (SA)	http://www.opa.sa.gov.au/
Office of the Public Advocate (VIC)	https://www.publicadvocate.vic.gov.au/
Office of the Public Advocate (WA)	https://www.publicadvocate.wa.gov.au/
Palliative Care Australia	https://palliativecare.org.au/
Parkinson's Australia	https://www.parkinsons.org.au/
Parkinson's NSW	https://www.parkinsonsnsw.org.au/
Patient Decision Aids (Decision Making)	https://www.safetyandquality.gov.au/our-work/partnering-consumers/shared-decision-making/decision-support-tools-patients
Step Up for Dementia Research	https://www.stepupfordementiaresearch.org.au/
The Public Guardian (NSW)	https://www.publicguardian.justice.nsw.gov.au/
Google searches	
Search 1	Research participation older people impaired decision-making capacity
Search 2	Research participation older people cognitive impairment
Search 3	Research participation older people dementia
Search 4	Research participation older people delirium

Supplementary file 2: Summary table of included studies

Author, year	Country	Aim	Participants	Data collection and analysis	Results
Structured interviews/questionnaires					
Herault, 2018	US	To compare older adults' responses about participation in research with decisional incapacity with their documented preferences and surrogate predictions	**101 dyads within a RCT of ACP for health care and research:** **Older adults (n=101):** 54% male; mean (SD) age 77 ± 4.5; mean (SD) schooling years 13 ± 5; self-rated health excellent or very good 56% **Self-selected surrogate (n=101):** 21% male; mean (SD) age 71 ± 9.1; mean (SD) schooling years 12 ± 4; relationship to older adult: spouse 74%, child 15%, other 11%; 76% living with older adult	Interviews with 3 vignettes of hypothetical studies (blood draw, physical exercises, drug trial) with older person's current decisions about participation compared to their preferences documented 6 months previously + surrogate predictions of current decision.	• 93% hadn't expressed their research preferences to surrogates • 44% would be bothered "a little" or "a lot" by their surrogate making research decisions inconsistent with their wishes • Current preferences "modestly" aligned with both ACP preferences and surrogate predictions; neither was superior (52-70% alignment, depending on study) • ACP under-enrolled for blood draw study and over-enrolled for physical exercise and drug trials; surrogates more often erred by under-enrolling
Cary, 2015	US	To compare spousal vs non-spousal caregivers' willingness to enroll a patient with AD in a trial and determine influence of research attitudes and caregiver burden	**Caregivers (n=103) of patients with probable AD (NINCDS-ADRDA Alzheimer's Criteria):** 31% male; mean (SD) age 62.8 ± 14.8, range 32-87. Non-Latino 97%, White 78%; spouse 54%, adult child 46% **Patients:** 31% male; mean (SD) age 78 ± 8.2, range 45-93	Structured interviews with vignette of hypothetical AD drug trial; ranking of likelihood of participating; demographics, QoL, dementia severity, ADLs, brief NIS, caregiver burdens and RAQ.	• 35% definitely or probably would participate; 36.9% possibly/might or might not/possibly would not; 28.2% probably or definitely would not • Willingness to enroll the patient positively associated with increased RAQ scores and being a spouse compared to being a child
Dunn, 2013	US	To examine whether and how proxies applied best interest and substituted judgement decision-making approaches for hypothetical AD drug trials	**Proxy decision makers for patients with AD (proxy-reported) (n=40):** 8% male; mean (SD) age 56.02 ± 11.2, range 36-86; relationship: adult child 75%, spouse 10%, other 15% **AD patients (n=40):** 65% male; mean (SD) age 82.9 ± 6.5, range 65-97; Lived: alone 15%, with others 45%, assisted living 18%, board and care 3%, nursing facility 18%, other 3%; Past research participation: yes 8%, no 92%	Questionnaire + interviews of proxies randomly assigned to consent process for 1/4 hypothetical AD drug trials of varying risks/benefits. Understanding assessed via MacCAT-CR, then questioned about decision-making approach.	• 78% endorsed BI (described as used in daily life and maximizing QoL); 68% endorsed SJ (described as knowing patient's values, honoring their wishes and prioritizing current preferences over past); 49% endorsed both approaches (described as honoring preferences while weighing burdens and benefits) • In a forced-choice, 58% endorsed BI, 43% SJ • No variables (study type, perceived risk, stage of patient's illness) associated with choice of approach
Black, 2013	US	To examine decision-making by individuals asked to participate in	**Persons with Alzheimer's, Parkinson's or other dementia from the Consent for Dementia Research Study (included**	Semi-structured interview about who made the current research decision and how, reasons for	• Subjects and surrogates often described current decision differently, diverse decision-making pathways and none predominated

		dementia research and their opinions on future proxy research decision-making, including preferred ethical approach	**three drug and three non-drug studies) (n=39):** 51% male; mean (SD) age 74.2 ± 8.8; MMSE score ≥24 54%, 19-23 30.8%, ≤18 15%; mean (SD) years education 14.6 ± 3.3; diagnosis: AD 67%, other dementia 31%, mild CI 10%, depression 8% **Surrogates (n=46)**: 74% male; mean (SD) age 63.1 ± 12.6; spouse 61%, son/daughter 22%, other relative 11%, non-relative 6%; mean (SD) years education 14.4 ± 2.4	participating, who should make future-research decisions and how (according to SJ, BI or something else). Eleven interviews abbreviated due to participant burden, inability to meaningfully respond or other communication difficulties. Illustrative quotes supplemented quantitative results	• Reasons for participating: potential benefit for subject (74% subjects, 80% surrogates); help others in future (62%, 53%); trust in clinician/university (35%, 16%); help surrogates/family member (18%, 40%); be informed of new treatments/other studies (6%, 11%); study required little of subject (6%, 7%); acceptable risks (5.9%, 4.4%); financial reasons (6%, 4%) • Future research decisions: 51% subjects nominated surrogates (mostly spouses), 39% nominated surrogates + other family members, 10% other family members; 55% surrogates (mostly spouses) nominated themselves; 73% of 33 pairs agreed • Preferred decision-making approach: BI (35% subjects, 42% surrogates); BI and SJ (18%, 20%), SJ (20%, 15%). 29% subjects and surrogates chose something else (e.g. impact on surrogate and/or other family members, feasibility of participating); six pairs agreed on approach (four BI, one combination BI and SJ, one SJ). For subjects with lower MMSE scores (≤18), 54% chose BI, as did 53% surrogates
Dunn, 2011	US	To describe proxies' reasons to enroll or not enroll a relative with AD in a hypothetical study	**Proxy and patient dyads (n=82)** **Proxies (n=82):** 22% male; mean (SD) age 70.2 ± 12.1; spouse 73%, adult child/grandchild 22%, friend/friend/another caregiver 22%* **Persons with AD or other dementia (proxy report of clinician diagnosis) (n=82):** male 77%; mean (SD) age 79.6 ± 7.2; living with proxy 89%, assisted living 4%, nursing home 2%, other 5%	Semi-structured interviews of proxies randomly assigned to receive written information for 1/3 hypothetical studies with varying risk and benefit (MRI/behavioral, drug, vaccine). Understanding assessed with MacCAT-CR, then asked whether or not they would enroll the person with dementia.	• 51% willing to enroll the person, 39% unwilling, 10% unsure. MRI/behavioral study: 72% willing, 24% unwilling, 3% unsure. Drug study: 52% willing, 41% unwilling, 7% unsure. Vaccine study: 27% willing, 54% unwilling, 19% unsure. Willingness differed significantly across three protocols • Societal benefits: improved/targeted treatments, better understanding of treatment effects (66%); enhanced knowledge of disease/progression (38%); earlier/improved diagnosis, understanding of cause (9%); help others in future (general) (6%); slow progression (6%) • Personal benefits: improve symptoms (38%); altruism/future benefit (30%); medical evaluation/attention (21%); compensation (20%); better diagnosis, more precise treatment (13%); none (9%)

					• Reasons to enroll: altruism (35%), direct benefits (18%), trust in institution (6%); educational (6%) • Reasons to decline: inconvenience (38%), concerns about risks (27%) and lack of interest by the person with dementia (9%)
Karlawish, 2009	US	To understand older adults' understanding of and attitudes to enrolling non-competent persons into AD research that does not benefit participants	**Adults ≥ 65 years south-eastern Pennsylvania (n=538)**; 41% male; mean (SD) age 76.8 ± 6.7	Structured interviews. Participants passing MacCAT-CR (93%) asked about willingness for proxy future research decisions and giving advance consent for two hypothetical AD studies (blood draw and blood draw + lumbar puncture) if they had AD. Those electing a proxy asked whether they would give them leeway to override advance consent. Other measures: SRS, HCSDS, RAQ, PTADS.	• Most (96%) willing to designate proxy for research decision-making; 83% willing to give advance consent to blood draw study, 48% to lumbar puncture study • Most willing to grant leeway to proxies over advance consent (81% blood draw, 70% lumbar puncture) • For participants wanting a proxy, advance consent plus granting proxy leeway meant 92% would allow enrolment in blood draw study and 75% in lumbar puncture study, advance consent alone would have decreased enrolment to 83% and 52%, respectively. • Associations with greater willingness: blood draw – spouse/partner proxy, more years of education, less financial burden; lumbar puncture - higher RAQ score
Karlawish, 2008A	US	To identify how alterations in trial attributes improved study partners' willingness to enroll their relative with AD	**Study partners** (n=108): spouse 52%, adult child 44%; 38% male; mean (SD) age 63 ± 14.5, range 32–87) **Patients with probable AD (NINCDS-ADRDA Alzheimer's Criteria; very mild to severe) enrolled in relevant trial**: mean (SD) age 78 ± 8.2, range 45–93; dementia severity mean ± SD, (range): NIS total (0–36) 8.5 ± 6.3 (0–27) and NID total (0–60) 9.1 ± 8.1 (0–42), basic ADLs (6–36): 9.3 ± 4.3 (6–26), IADLs (8–31): 20.7 ± 6.0 (8–31)	Structured interviews of study partners' willingness to enroll relative with AD in 21-month hypothetical drug trial, 50–50 probability drug vs placebo, 10 study center visits, 2% risk of cardiac damage. Understanding assessed via MacCAT-CR. Participants' reviewed eight trial designs with varying intervention risk, probability of placebo randomization, and location of and transportation to study visits and rated likelihood of allowing their relative to participate.	• Higher risk decreased willingness to participate • All other attributes increased willingness to participate (low risk, home visits, 67–33 chance of drug) • Home visits increased willingness to participate most of all • Willingness to participate in a trial without amenities 17%; adding home visits 27%; low risk, home visits and higher chance of active treatment 60%. • Value of reducing travel correlated with measures of AD severity, behavioral problems, travel time

Karlawish, 2008B	US	To examine experience and views of patients with AD and their study partners on proxy consent to a trial	**Patients with mild-moderate AD (NINCDS-ADRDA Alzheimer's Criteria; MMSE 12-26) enrolled in AD trial at 13/40 study sites (n=59):** 46% male; mean (SD) age 72.2 ±9.2; education mean years ± SD (range) 14.1 ± 2.8 (6-20); White 92%, African American 8%; non-Hispanic 97% **Study partners (n=60):** 43% male; mean (SD) age 64.3 ± 12.1; spouse 75%, education 15 ± 2.8 (8-20); White 92%, African American 8%; non-Hispanic 95%	Interviews of decision-making abilities via MacCAT-CR and psychiatric assessment, then about how study partners made decision to enrol the patient and attitudes towards proxy consent.	• No difference in study partners of decisionally capable vs decisionally incapable patients agreeing or disagreeing patient made decision on their own; study partners of decisionally incapable persons more likely to agree patient left decision to proxy • 85% study partners and 86% patients thought proxy consent was appropriate in general and for the patient • 59% study partners would enrol patient based on BI; 24% on SJ; 17% thought BI and SJ essentially the same • Most resolved conflict between the two approaches by choosing BI (73%) compared to SJ (26%)
Stocking, 2006	US	To examine patients with dementia and their proxies' views on ARDs and future proxy research decision-making	**Patient and proxy dyads within the 'Planning Ahead Together' (PAT) protocol[44] (n=149)** **Patients with Alzheimer's or other dementia (n=149)**: 38% male; mean (range) age 78.6, 52-94; MMSE mean (range) 19.8, 2-29; ≥ high school graduation 53%; self-reported health status good or excellent 69%; African American 33%, White 67% **Proxies (n=149)**	Separate interviews on previous research participation conversations with proxy, whether patients considered proxy the most trusted person for future decisions, and enrolment in five hypothetical studies of varying risk/benefit. Random dyads (n=69) participated in PAT protocol then talked to each other about earlier decisions.	• Discomfort with proxy decision making: 33% patients; discomfort increased with increased study risks (e.g. 9% blood draw vs 27% intracranial stem cell implant); more African-American respondents felt discomfort than did White (45% vs 27%). Reasons for discomfort: objection to study type (73%); autonomy (45%); problem with proxy (33%); need to confer with proxy (10%); proxy should share decision with others (8%). 16% patients with discomfort had previously discussed research participation with proxies compared to 30% without discomfort • Disagreement: 50% pairs disagreed in at least 1/5 studies (1=38%, 2=13%, 3=5%, 4=3%); 48% patient willing/proxy unwilling; 52% patient unwilling/proxy willing. Mean MMSE score of patients with one or more disagreements with proxy were higher than for patients with no disagreements (22 vs 18) • After PAT protocol, 83% patients agreed proxy should make future research decisions based on what he or she thinks best at the time rather than previously stated preference. Interpersonal

					patterns of resolutions included persuasion and assertion by either and planned future negotiation
Karlawish, 2002	US	To examine capacity, competency and reasons of patients with AD and their caregivers for enrolling in an early phase AD trial	**Patients with mild-moderate probable AD (NINCDS-ADRDA Alzheimer's Criteria) (n=15)**: mean (SD) age 72 ± 8.1, range 56-84 **Family caregivers (n=15):** mean (SD) age 64.9 (12.4), range 34–82 **Age- and education-matched non-demented older persons ('controls') (n=15)**: mean (SD) age 77 ± 4.5, range 69–86 to determine psychometric criteria to define capacity	Structured interviews assessing capacity to consent via MacCAT-CR and by experienced study coordinator (results not reported here), then reasons for enrolling or not enrolling in the trial and "How likely is it that your health will immediately improve as a result of participating in this research study?"	• 47% patients, 40% caregivers wanted to enroll; 20% patients, 53% caregivers did not; 33% patients, 7% caregivers unsure • Reasons for enrolling: potential benefit to patient health/well-being, desire to help others and/or contribute to scientific knowledge • Reasons not to enroll: need to talk to other family before making decision, time commitment/burden, concerns about disrupting patient QoL, medication risks, potential physical or mental discomfort • Belief participation would improve health: 'not at all likely' 50% patients, 40% caregivers; 'likely' 33%, 47%; 'extremely likely' 17%, 13%. Patients choosing at least likely had lower understanding scores than those choosing not at all likely
Elad, 2000	Israel	To investigate factors affecting caregivers' decisions to enroll or not enroll a demented patient in a drug trial	**Caregivers of "demented patients" of a memory clinic (n=29):** 19 enrolled the patient in an experimental drug trial, spouse 63%, 10 declined, child 70% **Patients (n=29):** "mostly female"; mean age 73.3; European 86%, Asian or African 7%, Israeli 7%; married 76%, widowed 24%; mean number of years since diagnosis: 3.98	Questionnaire about socio-demographics; patient function, cognition and behavioral problems; trial participation decision-making; perception of caregiving role.	• Enrolled patients "appeared" to have better function, cognition and emotional/mental condition • Reasons for enrolment: hope for patient's improvement (63%), stabilize/maintain condition (47%), helped to maintain hope (21%), contribute to science (11%), physician recommendation (11%), family pressure (5%), sense of responsibility for patient (5%) • Reasons for declining: concern about side effects (60%), doubts about drug efficacy (50%), concerns for physical burden for patient (30%) or caregiver (20%), disagreement among family members (10%), bad previous research experience (10%). • Everyone consulted with others for the decision; all enrolling and 47% declining consulted with other family members; 21% enrolling and 20% declining involved the patient • Most thought they received adequate information about side effects (95% enrolling, 95% declining) and potential benefits (74%, 89%) • More declining caregivers were usually concerned about medication side effects generally (89%) and

					in drug trials (70%), compared to 42% and 32% of enrolling caregivers, respectively • 11% enrolled previously participated in a drug trial vs 60% non-enrolled • Most caregivers believed they had the right (72% enrolling, 80% non-enrolling) and obligation (61%, 80%) to be responsible for the patient's treatment; and most (95%, 80%) felt that they did almost everything they could for the patient. Feelings of burnout were higher in non-enrolling caregivers (60%) compared to enrolling (11%)
Surveys					
Ries, 2019	Australia	To examine views of older adults about willingness to be involved in research if they had dementia-related cognitive impairment	**Older adults (n=174):** 46% male; age 60-74 n=126 (72%), ≥ 75 n=48 (28%); high school or below n=94 (57%), trade/vocational training n=46 (28%), tertiary/university n=24 (15%); knew someone with dementia 116 (76%) (friend 37%, other relative 34%, parent 21%, partner/spouse 8%). One (0.6 %) participant had dementia.	Questions on willingness to be involved in future research with dementia, motivating factors, preferred substitute research decision-maker and advance research directives (ARD).	• Over 90% agreeable to 12/13 research activities, less so for drug studies (60%) • Motivators: direct benefit (95%), could benefit others with dementia (94%); help scientists understand other diseases (90%) • Preferred substitute research decision-maker: substitute health-care decision-maker (88%), doctor/health professional on research team (78%), doctor/health professional external to research team (33%), independent legal body (29%) • 79% very or somewhat interested in making an ARD, 16% unsure, 5% not very or not at all interested
Calamia, 2016	US	To compare older adults' interest in and beliefs about drug vs other interventions for AD and factors associated with lack of interest in drug trial	**Older adults from Louisiana and surrounding states enrolled in a longitudinal study of brain aging (n=67)**: 36% male; mean (SD) age 70.4 ± 5.8, range 55–85. **Cognitively healthy** n=43 (64%), **with mild CI** n=24 (36%) (cognitive status determined from most recent parent study assessment last 12 months; mild CI based on RBANS)	Questions on current health, concerns about memory problems, interest in participating in studies with varying characteristics and beliefs about likely success of different interventions for chronic neurological diseases such as AD.	• Potential benefit for self and others strongly associated with increased interest in participation • 52% had decreased interest in drug trial with no significant individual predictors • Other study characteristics associated with decreased interest: receipt of lumbar puncture (68%) and daily (86%) or thrice-weekly (73%) study center visits • Drug interventions associated with greatest decreases in interest yet also thought more likely to be effective than meditation, acupuncture, yoga, computer-based interventions (but not exercise or dietary interventions)

Bravo, 2013	Canada	To identify factors influencing decisions to enroll a decisionally incapacitated close relative to a hypothetical study	**<u>Laypersons (n=1063):</u>** **Older adults (n=679):** 57% male; mean age 75.2 ± 6.9; education: high school 54%, < high school 20%, professional school/college 14%, university 12% **Informal caregivers of decisionally incapacitated older adults ('caregivers') (n=384):** 43% male; mean (SD) age 65.6 ± 12 (31-88); education: high school 46%, university 22%, professional school/college 20%, < high school 12% **<u>Professionals:</u>** **Physicians (n=495), researchers(n=177), IRB members (n=325)**	Survey questions about potential direct benefits, serious side effects and inconvenience to relative, potential benefits and inconveniences to relative, researcher reputation and potential benefit to others.	• Higher proportion older adults (61%) chose prospect of direct benefits for relative • Laypersons less frequently chose likelihood of adverse events as most influential compared to professionals (20% vs. 40%) • Researcher reputation more frequently chosen by laypersons than professionals (9% vs 2%) • Fewer laypersons high ranked possibility of serious side effects for relative compared to professionals (57% vs. 87%) • Inconveniences to relative more often considered least influential by laypersons than professionals (52% vs. 33%) as was possibility of side effects (8% vs. 1%) • No variables associated with older adult choices • Caregiver younger age associated with being influenced by potential for serious side effects
Jefferson, 2011	US	To describe participant reasons for enrolling in an AD research registry and barriers, incentives and variables associated with enrolling in additional studies	**Older persons (n=235):** male 40%; mean (SD) age 75.3 ± 8.1, range 58-99; 49% with mild CI (n=98) or dementia (n=18) (determined by procedures of the National Alzheimer's Coordinating Center for NIA-funded Alzheimer's Disease Centers)	Registry Participation Satisfaction Scale, IRMS, HCSDS, RAQ.	• Reasons for registry enrolment: advance AD research (56%), benefit family, friends, future generations (21%), personal concerns for memory (13%) • Barriers to study participation: insufficient time (30%), driving into city (28%), no transportation to research center (14%), no financial compensation for time (14%) • Incentives: transportation (61%), home visits (55%), compensation for time (50%) • Significant variables: Home-based visits endorsed by those who were older or had less formal education; non-White respondents more likely to endorse compensation as incentive; higher interest in participation correlated with higher RAQ score
Kim, 2009	US	To assess older Americans' views on surrogate consent for dementia research of varying risk and benefit and willingness for surrogate leeway to	**Older persons within the 2006 Health and Retirement Study (n=1515)**: 42% male; 51-59 years 32%; 60–69 years 35%; 70–79 years 20%; >80 years 12%; years of education <u>≤</u> 12 51%; 13-15 24%, <u>≥</u>16 24%; White 82%, Black 10%, Hispanic 6%, Other 2%; married 65%	Randomized to 1/4 surrogate-based research scenarios: lumbar puncture (n=374), new drug trial (n=398), vaccine (n=375), and first-in-human gene transfer neurosurgical (n=368) and asked whether society, one-	• For all scenarios, most believed society should allow family surrogate consent (68-83%), would themselves participate (57-80%) and would grant some or complete leeway to surrogates to override their stated preferences (55-67%) • Significant predictors of giving leeway to surrogates: being willing to participate, married, a woman, in excellent health, accepting gene

		override stated preferences		self or surrogate should allow participation.	transfer scenario (although not by those who considered religion very important) and feeling understood by their spouse or child.
Ayalon, 2009	US	To evaluate public opinion about participation in AD research and willingness for proxy consent	**Persons aged ≥ 50 years and their carers (any age) from 2006 Health and Retirement Study (n=1469)**: 42% male; ages 40-50 years 41%; 61-70 years 31%; >70 years 28%)	Participants given information about AD and AD research; randomized to 1/4 hypothetical studies with varying risks and benefits, questioned about wishes for proxy consent, whether society should allow families to make decisions in their place, degree of leeway given to close family members to go against their preference, socio-demographics	• Agreed to participate: 66%; agreed to proxy consent: 71%; give complete or some leeway to family members to go against their preferences (20% and 38%, respectively). • Only significant predictor of willingness to participate was research type: participants more likely endorsed moderate benefit/minimal risk and less likely endorsed minimal benefit/severe risk relative to minimal benefit/moderate risk. • Odds of agreeing to a proxy 9.42 times higher for those who had agreed to participate in research relative to those who refused
Kim, 2005	US	To explore views of older people at risk of dementia on surrogate consent for research	**Persons enrolled in an AD prevention trial, aged ≥70 years with at least one first-degree relative with probable dementia from four study sites (n=229)**: 59% male; mean (SD) age 77.3 ± 3.9; high school ≤ 19%, some college 28%, college 27%, postgraduate 24%; spouse/significant other 66%, lives alone 28%, other 5%; White 96%, Black 1%; Native American 0.4%, ethnicity not identified 3%	Information on AD symptoms, history, treatments, need for research, consent issues. Questions about acceptability of surrogate based research from societal, first-person and surrogate perspectives for 10 hypothetical studies of varying risk/benefit, risk categorization for each, RAQ, demographics, personal history.	• Majority (54%-95% depending on study type) thought all 10 surrogate consent studies should definitely or probably be allowed by society • More responders supported surrogate consent for lower risk studies and drug RCT (90%) compared to brain biopsy (56%) and gene transfer studies (54%) • Acceptability of surrogate consent highest from first-person perspective, then societal, then surrogate (significant in 23/30 (77%) scenarios) • Higher RAQ score only significant covariate for greater acceptability of surrogate-consent based research
Bravo, 2003	Canada	To elicit opinions about research participation decision-making for older cognitively impaired adults	**Laypersons (n=734):** **Older adults (n=300)**: 35% male; mean (SD) age 73.9 ± 6.7 **Informal caregivers of cognitively impaired patients (n=434):** 22% male; mean (SD) age 57.4 ± 11.9; 50% legal guardians) **Professionals (n=234):**	Questions about knowledge of relevant Quebec legislation; opinions about who should make research participation decisions when the elder lacks decision-making capacity, for hypothetical studies with varying risk/benefit; acceptability of soliciting a person with cognitively impairment for	• Previous research experience: older adults 11%, informal caregivers 26% • Overall: "few" respondents believed researchers could proceed without consent in any scenario; around 10%" thought cognitively impaired persons should not be solicited for research at all (30% for higher risk studies); most preferred a legal guardian and devoted relative or friend be involved; proportions favoring consent by just a close relative decreased as risk increased

			Researchers (n=98) and members of institutional review boards (n=136)	research; surrogate consent by a relative; socio-demographics and research experience.	• Group differences: laypersons more often wanted a relative or friend involved for higher risk studies; less often supported inviting people with decisional incapacity to research; less often permitted future surrogate decision-making for oneself, compared to professionals • Associations of increased permissibility to surrogates: older adults who were male or more willing to participate in research; informal caregivers who previously made surrogate decisions or more willing for cognitively impaired persons to participate in research
Qualitative studies					
Bardach, 2020	US	To understand what motivates individuals to become engaged and stay involved in longitudinal AD prevention and treatment trials	**Older persons who had participated in AD research at the Sanders-Brown Center on Ageing (n=28) and study partners (n=5):** 55% male; mean (SD) age 73.55 ± 5.14; Black/African American 3%, White, non-Hispanic 94%, White, Hispanic 3%; Cognitively impaired 15%; mean (SD) number of clinical trials 2.58 ± 1	33 face-to-face interviews focused on research participation motivations, experiences and views. Thematic analysis via constant comparative method.	**Activators:** Awareness of Disease; Memory Problems and Concerns **Motivators:** Know early and Be Proactive; Help and Provide Hope; Help the Future and Contribute to Society **Outside mediators:** Opportunity, Awareness and Ease of Participation; Comfort with Research **Re-enforcers:** Monitoring; Coping and Support; Mental Stimulation; Feeling of Value; Positive and Enjoyable Environment Findings informed the "AMOR (activators, motivators, outside mediators, re-enforcers) model of research engagement".
Austrom, 2011	US	To identify family caregivers of persons with FTD experience, attitudes, awareness, and understanding of research and brain donation	**Family caregivers (mostly spouse or adult child) (n=30):** 17.2% male; mean (SD) age 58.1 ± 12.8, range 25-76.5 of **persons with FTD:** mean age at diagnosis 62 years, range 47-89 Participants recruited via Association for Frontotemporal Degeneration and had varying access to FTD caregiver support groups and clinical research programs according to geographical location	Six semi-structured focus groups using a community-based participatory approach in three cities on experience with medical research, understanding of brain donation and its importance and effectiveness of communication with researchers. Grounded theory analysis.	**Willingness to participate**: interested and willing, but lacked knowledge of opportunities **When/how the issue of brain donation is raised**: considered inappropriate at first clinical meeting or at end stage; best time second or third visit after diagnosis **Who initiates discussion about brain donation**: no consensus **Who is involved in decisions about brain donation**: early discussion would allow the person with FTD to make his/her wishes known; considered not appropriate to discuss the issue in front of person once decision-making capacity was diminished; wide

					variability about who else (e.g. family, everyone involved, Rabbi) **Motivation for participating in brain donation:** obtain a definitive diagnosis, familial risk information and advance scientific knowledge **Lack of effective communication**: about procedure itself and what to do as death approaches **Barriers to research participation**: inappropriate and/or unmet expectations of clinical care, uncertainty about religious faith positions on organ donation, and inconsistent power of attorney state laws
Connell, 2001	US	To examine African-American and white caregivers' attitudes, decision-making and experiences of family members' participation in AD research	**Caregivers of a family member with AD or dementing illness enrolled in longitudinal clinical research at the Michigan Alzheimer's Disease Research Center (n=50):** 38 whites and 12 African Americans; 66.26% male; mean age 64; attended at least some college: 74% whites, 58% African Americans; spouse 63%, child 27%, other relative or friend 10%; mean time since first symptoms: 9 years	Six focus groups by ethnicity on making a decision to participate, experience with research process and recommendations for improving the process for future participants. Two additional questions for African American participants on barriers to/increasing participation. Content analysis.	**Benefits:** Access to Diagnosis, Care, and Treatment; Helping others; Support Received from Research Staff **Barriers:** No Direct Benefit; Procedures and Tests; Insufficient Time and Resources; Difficulty Accepting the Diagnosis; General Attitudes and Beliefs; Skepticism and Mistrust About Research in General and Specific Procedures **Recommendations**: Making Research Participation More Valuable and Rewarding; Increasing Research Participation
Sugarman, 2001	US	To examine proxy research decision-making and informed consent for patient-subjects with dementia	**Proxy and patient pairs from six dementia-related studies (n=49):** 46 Caucasian, 2 African-American, one Asian **Proxies (n=49**): male 40.8%; spouse (n=39), child (n=8), other relative (n=2); **patients with probable AD or other dementia (mild-severe) (n=49)**: male 42.9%, mean age 70.4, range 56-88, MMSE score 7-29, mean (SD) 21.1 $\pm$ 5.4	Initial (n=49) + follow-up at 2-4 months (n=46) semi-structured interviews about diagnosis, treatment, experience; recruitment, project, decision-making, advice to others re enrolment; informed consent process; experience with research participation; trust. Thematic analysis.	**Deciding to Participate:** shared (63%), made by proxy (27%) or patient (16%) (clearly and consistently attributed in one third of cases). Proxies tended to attribute decision to the patient when in agreement or risk was low, but would veto participation if did not agree. Most proxies who made decision to participate believed it was what the patient would have wanted, including for indirect benefits e.g. to feel "important again" **Reasons for Enrolling**: Clinical trials: hope for direct benefit, perception of nothing else available, desperation, and combined reasons (e.g. all of above plus hope of benefit for others); Genetic markers study (one-time blood draw in regular clinic visit): considered incidental, not interpreted as research, or forgotten. Reasons to participate were altruism, hope of secondary benefit (e.g. "best care"), legacy for

					children and grandchildren, and trust in physician or institution (which sometimes overrode proxies' desire to understand the study) **Burden of Decision-Making on Proxies**: Greater when there was higher study risk or invasiveness, and when dementia was mild or moderate (despite patient being able to participate somewhat in the decision) because it meant acknowledging the dementia. Lower when dementia was severe, as proxy was by then accustomed to making health-care decisions for the patient

Abbreviations: ACP: Advance care planning; AD: Alzheimer's disease; ADLs: Activities of Daily Living; ARD: advance research directive; BI: Best interests; CI: cognitive impairment; FTD: Frontotemporal dementia; HCSDS: Health Care System Distrust Scale; IADLs: Instrumental Activities of Daily Living; IRMS: Intrinsic Religiousness Motivation Scale; MacCAT-CR: MacArthur Competency Assessment Tool for Clinical Research; MMSE: Mini-mental State Examination; NIA: National Institute on Aging; NID: Neuropsychiatric Inventory Distress subscale; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; NIS: Neuropsychiatric Inventory Severity subscale; OR: odds ratio; PTADS: Perceived Threat of Alzheimer's Disease Scale; QoL: Quality of life; RAQ : Research Attitudes Questionnaire; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RCT: randomized control trial SD: Standard deviation; SR: supplementary references; SJ: Substitute judgement; SRS: Social Responsibility Scale
*Percentages totaled more than 100% but are reported here as within the article.

Supplementary file 3: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	pg. 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	pg. 4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	pg. 4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	The protocol was not registered, as PROSPERO do not accept scoping review protocols.
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	pg. 5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	pg. 5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary file 1 pg. 22
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	pg. 5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	pg. 5-6

Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	pg. 5-6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	pg. 6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	pg. 6-7; Figure 1 (pg. 21)
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	pg. 6-7
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Supplementary file 2 (pg.23-33)
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	pg. 8-10
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	pg. 10-14
Limitations	20	Discuss the limitations of the scoping review process.	pg. 14
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	pg. 14
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	pg. 2