Ethical understandings of proxy decision-making for research involving adults lacking capacity: a systematic review (framework synthesis) of empirical research

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Introduction

Research involving people who lack mental capacity, either as a result of a slow cognitive deterioration (as with conditions such as dementia), an acute event (such as a stroke), or never having had capacity to make complex decisions (such as those with profound learning disabilities), is vital if care for these groups is to be truly evidence-based. However, research involving groups considered to be vulnerable raises many ethical and legal issues: particularly with respect to informed consent for them to be included in a study (Harris and Dyson 2001; Shepherd et al. 2015; Sherratt et al. 2007; Sutton et al. 2003). The permissibility of proxy or surrogate decision-making for research involving vulnerable populations varies greatly between jurisdictions (De Martino et al. 2017; Veerus et al. 2013), however there is uncertainty whether proxies have sufficient moral authority to make such decisions (Wrigley 2007; Wrigley 2014), or if the ethical requirements can always be met (Sherratt et al. 2007). Proxy decision-making can be seen as comprising two main areas of ethical concern; the designation of the proxy who represents the person and why they are selected; and the nature of the decision-making itself. The ethical practice of proxy decision-making is an important issue, with substantial implications for the treatment and welfare of such individuals (Wrigley 2011). However, little is known about the ethical basis on which proxies act as decision-makers, or what factors are relevant in proxy decisions in practice, and there is a dearth of information or support available. Exploration and understanding of the ethical factors involved in these decisions, and interventions to inform and support those involved, are required in order for adults lacking capacity to have the opportunity to participate in research.

The use of systematic reviews to address issues in medical ethics is relatively novel, covering diverse issues (Megone et al. 2016; McCullough et al. 2007; Strech et al. 2008; Strech et al. 2013) and, although the practice has been widely debated, it has been suggested that they are a necessary development in the discipline (McDougall 2013). This review examined the empirical ethical issues surrounding decisions made by proxies for adults lacking capacity, specifically regarding decisions made about research participation. The primary aim of the review was to bring together empirical evidence about ethical issues in the practice of proxy decision-making for research participation. The review provides a synthesis of the empirical data, and the development of a conceptual framework.

Methods

This review synthesised the empirical data from primary research derived from qualitative, quantitative or mixed-methods studies which examined relevant ethical issues. The review followed the framework synthesis approach outlined by Gough (Gough et al. 2012), based on five stages from familiarisation with the data, to identifying an initial conceptual framework, indexing data, through to mapping and interpretation of the data to iteratively refine and develop the conceptual framework.

Ethical issues may have been clearly identified as such, or were ethical issues defined *a priori* from the literature - including proxy accuracy, burden, and comfort. An initial conceptual framework was developed utilising the review team's existing knowledge and preliminary searches of the literature, which informed the search strategy and search terms. The review was prospectively registered on PROSPERO

database of systematic reviews (CRD 42017054561). Ethical approval was not required for this review as no primary data were collected.

Search methods

A systematic search to identify relevant studies was performed following development of a search strategy with assistance from an information specialist, and piloting of appropriate search strategies. The search combined terms including: informed consent, research, proxy, surrogate, ethical principles, decision-making. The difficulties with identifying ethical issues using standard search filters have been noted elsewhere (Droste et al. 2010). Bibliographic databases were searched: Ovid MEDLINE, Ovid EMBASE, Ovid CINAHL, Ovid PsycInfo, ISI Web of Science, EUROETHICS and Scopus. Studies were limited to those in the English language, the search was not limited by date. Searches were conducted in January and February 2017. Supplementary searches were conducted including citation tracking, reference lists of included papers, and electronic table of contents (eTOC) of key journals for the last two years. The full search strategy is available in **Appendix 1**. Studies potentially eligible for inclusion were those reporting:

- Empirical research, using qualitative and/or quantitative methods, aimed at understanding proxy consent to research participation for adults lacking decision-making capacity
- Studies that report patients' or researchers' views/experiences of proxy consent/agreement for research participation
- Ethical issues arising in obtaining proxy consent/agreement for research participation (which includes proxy accuracy, discrepancy, and comfort)

Studies were excluded if they reported the views of clinicians, or did not include consent for research (such as treatment only), were protocol papers, or were not empirical research (such as argument-based normative papers).

Study selection

Titles and abstracts from the initial searches were screened based on the inclusion criteria by one researcher (NAME REMOVED FOR PEER REVIEW), and a sample of around 20 papers from the initial searches were reviewed by three researchers (NAMES REMOVED FOR PEER REVIEW) to ensure the accuracy of the application of inclusion and exclusion criteria. Full text of all potentially relevant studies were retrieved and screened using the same process (NAMES REMOVED FOR PEER REVIEW). Data from the included studies were independently extracted by two of the authors (NAMES REMOVED FOR PEER REVIEW) using a review-specific form developed following piloting on three heterogeneous papers. Quality assessment was conducted to assess the methodological rigour of included studies using standardised frameworks appropriate to the different types of study reviewed (Downes et al. 2016; CASP 2013). Studies were not excluded from the evidence synthesis based on quality assessment alone, as is increasingly the case for qualitative reviews (Carroll et al 2011). Quantitative studies were small with highly heterogeneous populations and measures. Meta-analysis was not feasible, therefore narrative summaries of the quantitative data were created. Data from the qualitative studies and narrative summaries were extracted and entered into NVivo 11. The number of studies reviewed and included/excluded are reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009).

Development from the preliminary conceptual framework to the final model

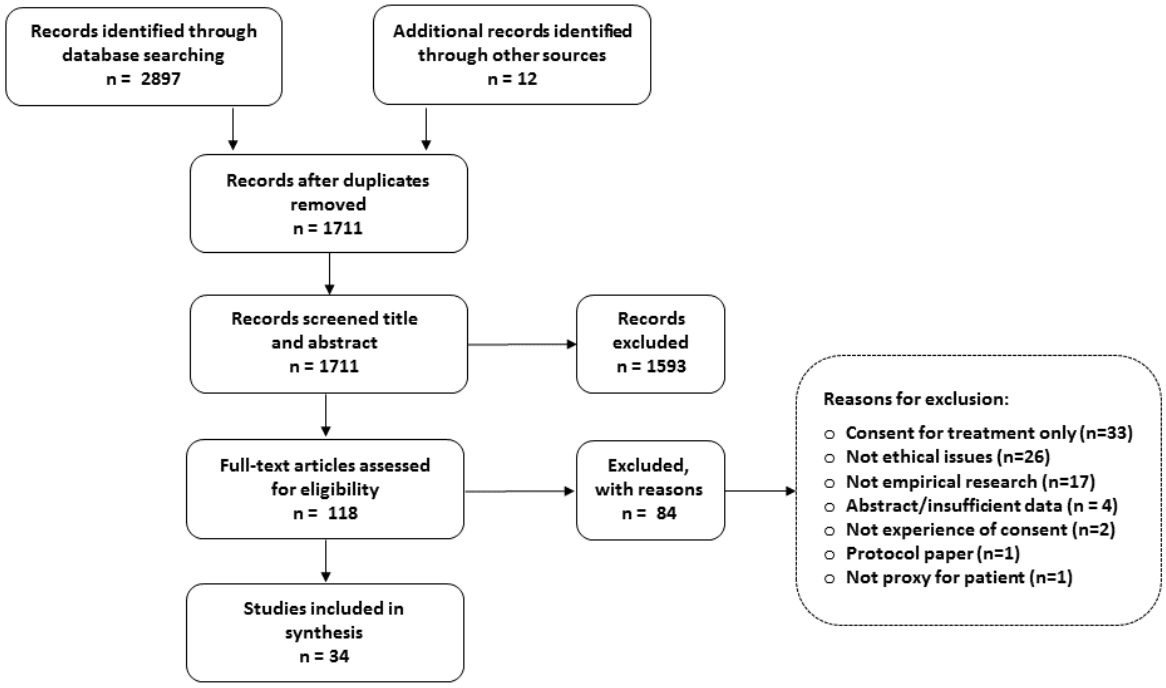
Initial candidate themes were identified through a comprehensive review of the normative and empirical bioethical literature. A preliminary conceptual framework representing these themes was agreed by the review team during development of the study protocol. Data were coded thematically by one of the researchers (NAME REMOVED FOR PEER REVIEW) and coded data were reviewed by two additional researchers (NAMES REMOVED FOR PEER REVIEW). This review by two other researchers allowed the team to consider the validity of the coding and achieve consensus on the coded data. Adequacy of the initial themes (as opposed to codes) was assessed by three researchers (NAMES REMOVED FOR PEER REVIEW) after coding of data extracted from seven studies. As themes and contexts expanded, and new themes emerged, the framework was developed, and data were coded iteratively. Definitions for each theme were developed and refined through discussions between the review team who agreed the inclusion of new themes. Data were mapped and aggregated under each theme. Proxy decision-making is highly complex and contextualised; therefore, attention was paid to the context surrounding each theme and individual study.

Once the coding was completed, and adequacy of the final themes was confirmed, a revised conceptual framework was developed by the review team building on the earlier model. The revised framework, comprised of two dimensions, outlines the distinctive role and function of each theme and the complex relationships that exist between them. The relative contribution of each study to the synthesis was summarised and tabulated under key themes of the framework.

Results

The search identified 1711 unique citations, of which 118 were assessed as meeting the inclusion criteria when the title and abstract were reviewed. Following review of the full text, 84 were excluded, with 34 studies remaining for inclusion in the review.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram



Characteristics of the included studies are summarised in **Appendix 2**. The studies were published between 1986 and 2017. Almost all of the studies were conducted in North America (n=32). The majority of the studies involved research into conditions characterised by cognitive decline (dementia n=19, older people in long-term care n=2), followed by an acute event (critical care n=11, neurological emergencies n=2). No studies involved those whose disabilities may have resulted in never having had capacity to make complex decisions. Only five of the included studies explored experiences of proxy decision-making in real-life situations, the majority examined

hypothetical decisions. Sample sizes varied greatly between the studies, ranging from 10 to 1,515 participants. The studies generated both qualitative and quantitative data: research methods used in the studies were evenly divided between structured or semi-structured interviews and survey/questionnaire instruments, one study combined survey and interview methods, and one study combined survey and discussion group methods. Three studies evaluated interventions intended to improve proxies' deliberation or decision-making processes.

Key themes emerged (**Appendix 3**): four that relate to the ethical framing criteria of decision-making – 1) the use of a substituted judgement, 2) use of best interests, 3) a combination of substituted judgement and best interests, and 4) an alternative basis or 'something else'; and four that can be considered to be active elements of proxy decision-making – 1) knowing the person, 2) relationship, 3) accuracy of the decision, and 4) balancing the risks, benefits and burdens, and attitudes towards proxy decision-making. The studies which generated data coded to each theme were tabulated (**Appendix 4**).

Ethical framing criteria of proxy decision making

Proxies' decision-making was characterised by uncertainty, given the set of alternatives and possible consequences of each choice, both for the proxy and the patient. The proxy's approach to decision-making emerged as a decision frame, which was dependent on their conception of the decision, potential outcomes, and consequences associated with a particular choice (Tversky and Kahneman 1981). Differences in the proxy's formulation of the decision, and variables involved such as the perceived risks and benefits of the research, caused significant shifts in how the

proxy was orientated to the decision, which provided a foundation for how the decision was made.

Data on the framing intent of proxy decision-making was grouped into four domains: utilising substituted judgement, a best interests approach, a combination of both substituted judgement and best interests, and 'something else'. These domains were identified from the questionnaires, survey items, and qualitative themes reported in the included studies, and map onto the proxy decision-making 'standards' described in the bioethics literature (Sugarman and Sulmasy 2010). In order to meet these standards, decision-making would need to fulfil certain criteria, such as decision-making centring on maximising the well-being of the patient could be thought of as meeting the best interests standard, or basing it on the views and preferences would meet the substituted judgement standard.

Six of the included 34 studies explicitly presented data on the framing criteria.

Substituted judgement

A substituted judgement was characterised by the proxy attempting to, or being directed to, make the decision that the person would themselves have made if they had capacity, as illustrated by this participant who had dementia:

> *'I would want her hopefully to make that decision on what she thought I would think. OK. Not what she thinks, not what somebody else thinks, but what I think…what she thinks I would have done'* (Black, Weschler, and Fogarty 2013, 361).

There were notably lower levels of support for the use of substituted judgement, in comparison to the use of best interests. 9% of proxies for people with dementia chose only substituted judgement as their preferred criterion of proxy decision-making for research (Black, Weschler, and Fogarty 2013), 15% of patients with

dementia preferred substituted judgement alone (Black, Weschler, and Fogarty 2013), and 24% of proxies would base the decision on 'what the patient would want' (Karlawish et al. 2008). Despite this, when proxies were asked what criterion they had used for deciding about a proposed hypothetical study, around half stated they would decide primarily based on substituted judgment (Dunn et al. 2012). Proxies described using 'substituted judgment' in other decisions they made for the person (Dunn et al. 2012), although some were able to distinguish decisions about research from other types of decision, and reported that they used a different ethical criterion for different types of decision:

> *'for research I would make it based on what I thought she would want. If it was treatment, I would probably make it based on what I thought was best for her, but for research, I'd probably go with what I thought she would want'* (Black, Weschler, and Fogarty 2013, 361).

Best interests approach

A best interests approach focussed on what would maximise the person's welfare or interests, as illustrated by this subject's views: *'what he thinks is best for me I would say. In that situation, I can't want or not want'* (Black, Weschler, and Fogarty 2013, 361).

The use of only 'best interests' approach when deciding about research participation was supported by around half of proxies (Black, Weschler, and Fogarty 2013; Dunn et al. 2012) and a third of patients with dementia (Black, Weschler, and Fogarty 2013, 361) in largely hypothetical scenarios. However, the majority of proxies for people with dementia answered that they would decide based on 'what would maximise the patient's well-being' in a study involving actual research decisions (Karlawish et al. 2008). Proxies reported being accustomed to making everyday

decisions using a ‘best interests’ approach (Dunn et al. 2012). They reported the use of a ‘best interests’ approach to research decisions, even where this might override what the person’s own decision might have been (Dunn et al. 2012), perhaps perceiving benefits from the research that justified overriding the person’s wishes in order to promote their well-being. Proxies clearly saw themselves as holding a protective role (De Vries et al. 2010; Muncie et al. 1997; Warren et al. 1986). Some proxies did not appear to distinguish between the interests of the person and those around them:

> *‘Based on what would be best for him, not on what he would decide. I’ve made most of my decisions in life as to what would be best for him. What would be best for the family. There is no other way to decide* (Black, Weschler, and Fogarty 2013, 361).

Use of a combination, or another criterion – ‘something else’

Moderate levels of support were given by proxies and patients for using a combination of substituted judgement and best interests for proxy decisions. 20% of proxies for people with dementia would use a combination of best interests and substituted judgement, and 18% of patients with dementia supported a combination of both criteria (Black, Weschler, and Fogarty 2013). Although some proxies conflated different framing criteria, reporting that they would use a combination, because that is what the person themselves would have used to decide:

> *‘well the two might not be different. What’s best for me and what I would do might be the same thing and I think that’s what she would make the decision on. She would consider both*’ (Black, Weschler, and Fogarty 2013, 361).

In Dunn et al (Dunn et al. 2012), nearly half of the proxies agreed or strongly agreed with both, and spoke about the desire to incorporate both criteria in considering research participation. Most proxies in Karlawish’s study described a complex

weighing process of their substituted judgement, with their preferences, and with the person's own current preferences (Kalrawish et al. 2001).

In Black et al (Black, Weschler, and Fogarty 2013), proxies and people with dementia were able to indicate that they supported another criterion - neither best interests nor substituted judgement but 'something else'. 29% of proxies chose this third option, which often incorporated multiple concerns, such as considering whether it would be feasible for the person to co-operate with study procedures or to manage the travelling to study visits. The same proportion of people with dementia chose the 'something else' option (29%), some wanting proxies to consider their own interests or those of family members, or following consultation with others (Black, Weschler, and Fogarty 2013). Proxies in Dunn et al explicitly described the need to weigh numerous factors concurrently, which would include the person's preferences and personality before becoming ill, potential societal benefits, and current quality of life (Dunn et al. 2012).

Active elements of proxy decision making

Themes emerged from the data that were considered to be characteristics or elements of decision-making, that functioned to a greater or lesser extent in the decision-making process depending on the context, the relationship between the patient and their proxy, and the attitude of the proxy themselves. They actively directed proxies to accept or reject the option of research participation by serving as factors to be weighed in the decision-making process, as indicators to the proxy for how they should frame the decision, and sometimes as justifying reasons for the decision itself.

Relationship between the patient and the proxy

Participants reported that the choice of who acted as their proxy was important, and participants commonly used aspects of their relationships when they reported their views or experiences of proxy decision-making for research. The choice of proxy was reported as relevant to proxy decision-making in three studies (Berger et al. 2005; Del Giudice et al. 2009; Sachs et al. 1994). One study that reported reasons for endorsing proxy consent centred on various aspects of trust, the closeness of their relationship and, in some cases, their previous experiences with decision-making for them (Sachs et al 1994). Similarly, another study overwhelmingly cited trust and family closeness for reason for choosing the individual identified as their proxy, with love and closeness also mentioned, and many reporting that their trust was based on the proxy's performance in a past crisis (Berger et al. 2005). The participants also generally saw no distinction between acting as a proxy for decisions about care or treatment and acting as a proxy for research, all participants presumed the same person would act as proxy for both types of decision (Berger et al. 2005). Notably, one study found there was low levels of support for a professional acting as their proxy, only 7% would allow a healthcare provider to provide consent on their behalf, compared to 88% who would allow a family member to provide consent (Del Giudice et al. 2009).

Some participants discussed the reciprocal nature of family relationships that are built on mutual understanding and responsibilities. Older people in Berger et al's study reported that they had chosen a family member to act as proxy on a mutual and relational basis: *'She's most familiar with what I want, as I am with what she wants. She's really the one I trust the most'* (Berger et al. 2005).

Two studies reported that proxies consulted other people to gain consensus before making a decision about research participation. Black et al included some proxies who had made actual decisions on behalf of a person with dementia, some of whom consulted with other family members before deciding (Black, Weschler, and Fogarty 2013). Warren et al's study with proxies for nursing home residents found that 60% of proxies consulted others before making a decision, of these about half (27% of the total) consulted medical professionals (Warren et al 1986).

Accuracy of the 'decision'

Much of the research focussed on whether proxies can accurately predict what the patient would decide about participating in a hypothetical research study (Bolcic-Jankovic et al 2014; Bryant et al 2013; Ciroldi et al 2007; Coppolino and Ackerson 2001; Muncie et al 1997; Newman et al 2012; Stocking et al 2006). These studies use the patient's own prediction as the correct decision or the 'gold standard', against which the proxy's decision or prediction is measured as a form of 'diagnostic test' (Coppolino and Ackerson 2001). In order to determine the accuracy of the proxy's prediction or decision, the researchers have made the assumption that these are conceptually the same as the patient's own decision. Proxies' decisions that are incongruent with the patients' own decisions are said to be either 'false positive' where the proxy would have enrolled the person when they would not have wanted to participate, or 'false negative' where the patient would have wanted to take part but the proxy declined to enrol them.

Accuracy varied, with 76% reported in one study (Bryant et al. 2013). Similarly, in Ciroldi et al the patient-proxy discrepancy rate varied between 32% - 42% (Ciroldi et

al 2007), and Newman et al found that the overall percentage of discrepancy increased as the perceived risk associated with the study rose (Newman et al. 2012). Stocking et al found that 49.7% of patient-proxy dyads directly disagreed about patient enrolment in at least one of the five hypothetical research projects described (Stocking et al. 2006). Of these disagreements, 47% involved the patient willing to enrol and the proxy was unwilling to enrol them, and 52.2% of disagreements reflected the reverse, proxy willingness and patient unwillingness (Stocking et al. 2006). A study that examined the accuracy between patients who had been in critical care and their proxies, showed that most proxies would respond in accordance with patients' wishes, although patients were more likely to agree to participation in the genetic research than their proxies would have allowed (Bolcic-Jankovic et al. 2014). Muncie et al found that the agreement between proxies' decisions and the patients' decisions was no higher than the decisions of randomly assigned, unrelated, proxies would be (Muncie et al. 1997).

Confidence and certainty

Three studies reported data relating to confidence in the proxy's ability to decide in accordance with the person's wishes or the certainty that the decision was in accordance with their wishes, all were studies which involved research in acute care settings. Bryant et al's study with emergency department patients and their proxies found that both patients and proxies indicated relatively high degrees of confidence in the decisions they were making (Bryant et al. 2013). Confidence was associated with accuracy in a study with critical care patients and their proxies, which found that 80% of proxies who were confident responded in agreement with patients' wishes (Bolcic-Jankovic et al. 2014). Both proxies and patients showed overwhelming confidence in the proxy's ability to make a decision based on the patient's wishes:

53.2% of proxies were very confident, 41.6% moderately confident, with only 5.2% not very or not at all confident (Bolcic-Jankovic et al. 2014). Patients also showed high levels of confidence in their proxy making a decision consistent with their wishes: 76.2% were very confident, 18.2% moderately confident, and only 5.1% not very or not at all confident (Bolcic-Jankovic et al. 2014). The only factor that influenced patients' confidence in their proxies was whether they had prior discussions with them, however having a prior discussion was not significantly associated with proxies' confidence in their own ability (Bolcic-Jankovic et al. 2014).

Confidence was also associated with accuracy in Coppolino's study with elective cardiac surgery patients and their proxies, which found that agreement was higher between patients and proxies where proxies felt "absolutely certain" or "certain" about their predictions (Coppolino and Ackerson 2001).

Leeway given to proxy

Eight out of the 34 included studies explored the amount of freedom or leeway the person would give their proxy when it comes to making decisions about research on their behalf. A majority of respondents were willing to give some or a complete amount of freedom or leeway to go against their currently stated preferences about future research participation, although it varied by scenario (Aayalon et al 2009; Karlawish et al 2009; Kim et al 2009; Kim et al 2013). Kim et al found that the leeway given to a close family member by caregivers for people with dementia varied little by study type, with 37% allowing no leeway, 57% some leeway, and 17% giving complete leeway (Kim et al. 2013). The main reasons given for granting leeway were that the proxies would have more or better information in the future, that the ratio of the risks/burdens vs. benefits may be different at the time of the study, or that the

proxies may be able to better assess the risks at the time (Kim et al. 2013). Whereas those who would not give leeway perceived leeway as violating their right to make decisions for themselves (Kim et al. 2013).

Knowing the person

Five studies reported that knowing the person's wishes and values were relevant factors in proxy decision-making for research (Berger et al 2008; Burns et al 2017; De Vries et al 2010; Dunn et al 2013; Overton et al 2013). Proxies described basing their decision-making as based primarily on their overall 'knowledge' of the person's values, wishes, past behaviours and decisions, or some combination of these, by virtue of the relationship that exists between them (Dunn et al. 2012). Fidelity to the person's wishes was achieved through representing their historical values, whether expressed in past conversations and behaviours, or embodied in patients' character traits (Overton et al. 2013). Other proxies cited the need to 'honour' the person's life, values, and wishes— even if they personally disagreed with the decision (Dunn et al. 2012). However, in many cases, their explicit wishes were not known to proxies (Burns et al. 2017), and few proxies (30%) had previously discussed research preferences (Coppolino and Ackerson 2001).

Many proxies felt that decisions about people with dementia taking part in research should be based on a written document expressing their willingness to participate that had been made before they lost decisional capacity (De Vries et al. 2010). One study found that 88% of participants stated that their family could agree for them to participate in research in the absence of a research advance directive, and 80% stated that their families could enrol them in research that may potentially benefit

them even if their advance directive opposed enrolment in research (Wendler et al. 2002).

A commonly cited principle was altruism (De Vries et al 2010; Dunn et al 2011; Mehta et al 2012; Sachs et al 1994; Sugarman et al 2001), described as the desire to help research or to help others, to be a 'good citizen' (Sugarman et al. 2001), or the desire for future societal benefits (Dunn et al 2011). However, proxies were acutely aware of the moral difference between deciding for oneself and deciding for others based on altruistic motives (Dunn et al 2011). Altruistic motives were a joint motivation for the person and proxy (Dunn et al 2011), where proxies may have experienced altruism 'by proxy', although it was sometimes considered to be a secondary motivation, following the hope that the person themselves would benefit from the research (Sugarman et al. 2001). Some proxies were aware that their own children or grandchildren may someday develop the same disease (Alzheimer's disease) and the trial might one day benefit them (Sugarman et al. 2001) – as a form of 'selfish altruism'.

In one study, proxies for people with dementia reported that using the person's character as the basis of the decision was problematic, as the changes wrought by the disease made it impossible to use 'who' the person was in the past to make decisions today (De Vries et al. 2010). Proxies contrasted the personality and decision-making preferences of the person prior to developing dementia versus their view of the person's current preferences (Dunn et al. 2012). Proxies had difficulties with the complex ethical issues, such as reconciling the need for research in order to develop new therapies, with their values relating to autonomy, experiencing and inflicting pain, and their responsibilities as carers (De Vries et al. 2010). Current preferences were frequently described by the proxies as taking precedence,

regardless of prior preferences. Proxies believed that if the person currently would prefer not to participate, there was a certain point beyond which they would not be willing to 'force them' to participate (although the nature and extent of any such 'force' was not reported) (Dunn et al. 2012).

Balancing risks, benefits and burdens, and attitudes towards proxy decision-making

A number of studies addressed issues of perceived risks and benefits associated with participating in different type of studies, and study-related procedures that were considered burdensome. Dunn et al's survey of community-dwelling people aged 50+ found that study type was associated with willingness to participate, and to have a proxy to make decisions about research for them (Dunn et al. 2012). Participants were more likely to endorse a moderate benefit and minimal risk scenario, and less likely to endorse a minimal benefit and severe risk scenario, when compared to the minimal benefit and moderate risk scenario. Proxies for people with dementia commonly cited concerns about potential risks when interviewed (Dunn et al. 2011). In one of the few studies that involved a real-life decision about a research study the patient was actually being considered for (rather than merely hypothetical), if the proxies for critical care patients perceived that the risk of participation was too high, or felt patients may not benefit from participation, they did not contemplate further (Burns et al 2017).

Comfort with proxy decision-making

Four studies explored comfort with proxy decision-making on behalf of oneself or another person, or comfort with making decisions on others' behalf. Dubois et al

questioned five groups, including older people, informal caregivers, physicians, ethics board members, and researchers, using four scenarios (Dubois et al. 2011). They found that as the study's risk benefit profile becomes less favourable, the proportion of participants expressing comfort with proxy consent decreased in all groups (Dubois et al. 2011). Where studies involved serious risks with greater potential benefits, their comfort with proxy consent was lower when the proxy was neither appointed nor designated, and higher when designated in a healthcare advance directive with instructions regarding research participation (Dubois et al. 2011).

Stocking et al examined patients' own comfort with proxy decision-making for research for themselves, and found this also varied by study type (Stocking et al. 2006). Patients with dementia were presented with five hypothetical studies, 32.9% said they would not be comfortable with proxy enrolment decision making in one or more of the hypothetical situations described, and their discomfort increased with the risk of the hypothetical study from 8.5% for a blood sample to 26.5% for intracranial stem cell implant (Stocking et al. 2006).

Karlawish interviewed both patients with Alzheimer's disease and their proxies and found high levels of comfort with proxy decision-making for research in both groups (Karlawish et al. 2008). 85% of proxies thought that proxy consent was appropriate in general and also for their relative if they were unable to provide their own informed consent (Karlawish et al. 2008). The proxies' reasons included their role in making other decisions for the patient such as finances and treatment, and the patient's wishes to contribute to research. 86% of patients showed similar consensus as their proxy. Reasons commonly cited were that the proxy had their best interest in mind, or knew of their intentions (Karlawish et al. 2008).

Burden of proxy decision-making

Six studies provided data on the burden of proxy decision-making for research. Proxies for people with dementia recognized that having the choice of whether or not to enrol the patient in research added to their burden. Proxies were acutely aware of the moral difference between deciding for oneself and deciding for others (De Vries et al. 2010). Studies with proxies in critical care found that the burden varied by study type or level of risk. Barrett et al showed that few proxies reported it would be a burden to be involved in the consent process for the low risk (baseline) study or for the study involving two standard treatments (Barrett et al. 2012). However, a greater proportion felt it would be a burden to participate in decision making for the higher-risk treatment and for the scenario where a decision was needed quickly (Barrett et al. 2012). Similarly, Mehta et al reported that 20% of proxies found the process very burdensome in the higher risk and shorter enrolment window scenarios, and up to 30% were very uncomfortable making the decision (Mehta et al. 2012).

Similarly, the perceived risk also affected the burden experienced by proxies for people with dementia (Sugarman et al. 2001). Burden could be decreased if the patient themselves was able to play a meaningful role in the decision, however some reported that, even when the person could be involved in the decision, the burden was high because the decision to participate meant acknowledging the dementia:

> *'Well, it felt like . . . you was saying [sic] that you knew that he wasn't going to be capable of making his own decisions. You know that it hurts to know . . . that he's getting to that point that he can't even make decisions for himself.'* (Sugarman et al 2001, 1115).

One study reported that burden may be experienced as a result of feeling that other family members would not agree with their decision or would 'blame them' for enrolling the person (Burns et al. 2012).

Acceptability of proxy decision-making for research

Seven of the included studies examined acceptability of proxy decision-making, either from a societal perspective, for themselves at some future point, or as proxies on behalf of another person. A survey of 1469 community-dwelling people aged 50+ in the US showed high levels of support, with 70.7% agreeing to have proxy-informed consent for themselves (Aayalon et al. 2009). A study with 240 people who had survived a critical illness reported that, compared to alternative consent models, most patients (76%) selected ''consent by surrogate decision-maker prior to enrolment'' as their preferred framework, regardless of the level of study risk (Scales et al. 2009). In Sachs et al's study with different populations, those considered the 'well elderly' group reported a variation depending on the perceived risk of the study, with willingness to accept proxy consent declining from the blood sample study, to brain autopsy, to medication trial, to surgery/medication study (Sachs et al. 1994). Comments about proxy consent from this group were very similar to those of the people with dementia, one participant who would refuse to allow a proxy to decide about the surgery/medication protocol said: *"It's too dangerous for someone else to decide"* (Sachs et al. 1994, 408)

Overwhelmingly, proxies reported that they are keen to be involved. The majority (90 %) of proxies for critical care patients wanted to be involved in decision making about research on their behalf (Barrett et al. 2012). Although, acceptability of involvement in the consent process was less in the higher risk studies and those

mandating less time to make a consent decision. Similarly, Kim found that 92-94% of proxies for dementia patients supported proxy consent for the less invasive study, compared to 53% - 62% for the most invasive of the hypothetical research studies (Kim et al. 2010). An earlier study led by Kim found that risk also influenced the older people they surveyed (Kim et al. 2005). They found that acceptability of proxy consent-based research was strongly influenced by the level of perceived risk, resulting in an adjusted odds of finding a minimal risk study acceptable for proxy consent 60 times relative to that for high risk studies (Kim et al. 2005). However, in their 2009 study Kim et al found most of the 1515 community dwelling aged 50+ were supportive of allowing families to make proxy consent decisions for dementia research (67.5% to 82.5% by study type), even for a first-in-man gene transfer study nearly 68% stated that society should allow families to make such proxy decisions (Kim et al. 2009).

Most (96%) community-dwelling older people were willing to designate a proxy for research decision making (Karlawish et al. 2009).

Willingness to participate

Seven studies explored participants' willingness to take part in research should they lose capacity. Kim et al found that, generally, older people's levels of acceptability for proxy consent for themselves were comparable to their willingness to participate in a research study, although for one hypothetical study (a vaccine study) a significantly greater proportion would allow proxy consent than would themselves want to participate (Kim et al. 2009). Patients in emergency departments and other members of the public reported a willingness to participate in a hypothetical SAH trial, with 34% definitely participate, 20% probably participate, 22% possibly participate, 5%

probably not, and 10% would definitely not participate (9% could not decide) (Del Giudice et al. 2009).

The vast majority of participants in Wendler et al were willing to participate in clinical research if they lost the ability to consent, ranging from 80% - 99% depending on study type and perceived level of risk or benefits (Wendler et al. 2002). Exploratory analyses found no significant associations with characteristics such as sex, age, religion, and previous execution of a healthcare advance directive. Critical care patients were significantly less likely to participate in research as the perceived risk associated increased, with no associations found between their length of stay in critical care, age, race, or gender (Newman et al. 2012). Similarly, older people interviewed in Berger et al were reluctant to consider research involving taking experimental drugs or those with serious known side-effects (Berger et al. 2008).

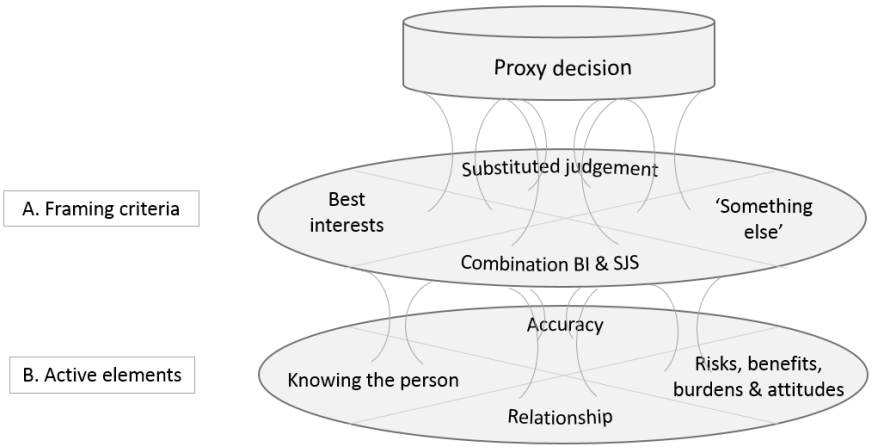
Proxies' willingness to participate in research themselves was associated with their willingness to enrol the patient as their proxy decision-maker. Clarridge found that the likelihood of the proxy for a critical care patient participating in research influenced the likelihood of that proxy permitting the patient to participate in research (Clarridge et al. 2015). Muncie found that proxies' decisions for their own participation were significantly associated with their 'guesses' of the patient's decision, and therefore with their decisions for the patient (Muncie et al. 1997). Consequently, for each hypothetical study, the proxies' decisions for the patient were significantly more frequently in agreement with the proxies' own decisions for themselves than with the patients' decisions to participate. Similarly, 80% of proxies for nursing home residents would be willing to participate in the hypothetical study, and proxies who would take part themselves were significantly more likely to give consent for the care home resident they represented (Warren et al. 1986).

Three studies found that proxies were more likely to enrol themselves, than would be willing to agree for the other person to take part. Both Sachs et al (Sachs et al. 1994) and Kim et al (Kim et al. 2013) found that proxies as a whole were more willing to participate themselves than they were willing to give proxy consent for their relative, regardless of study type. Lim found that this varied by study type, with proxies being five times more likely to have a favourable opinion for themselves as the patient in the lower risk studies, and six times more likely for the higher risk study (Lim et al. 2013).

Discussion

This systematic review suggests that proxy decision-making for research can be thought of as being comprised of two dimensions; the framing criteria used by the proxy to make a decision, and the active elements that feature in the decision-making process itself. The relationships between the framing criteria and the active elements are complex, operating on a number of different levels, as components interacting between themselves, with both explicit and implicit modes of interaction, and which may be context dependent. The conceptual framework provides a synthesis of the concepts and perspectives that emerged from the empirical data, to describe the relationships between the framing criteria used by the proxy, and the active elements of decision-making (**Figure 2 Conceptual framework**).

Figure 2. Conceptual framework



Proxy utilisation of the elements and criteria is highly context-dependent. The active elements both support, and are influenced by, the framing criteria used by the proxy in their decision-making. The relationship between the person and their proxy has a fundamental role: both as the key that allows the proxy to make decisions on behalf of another person, and the tool to guide them towards a decision.

The ethical framing criteria (**Figure 2, A**) play a structural role which forms the basis, or orientation, from which the proxy engages in decision-making, and shapes the nature of the decision. The decision frame used by the proxy was dependent on their formulation of the decision, the potential outcomes, and consequences. It directed the proxy's perspective on decision-making – whether they attempted to determine what the person's decision would have been through 'standing in their shoes' to meet the criteria of a substituted judgement, or whether they provided their own determination of what would derive the maximum benefit for the person and would therefore be in their best interests. Where proxies reported the use of a combination of both criteria, it was either expressed as hope that the decision they made would match the outcome of both, or that if they made a substituted judgement it wouldn't be *against* the person's best interests. However, the low levels of support for both substituted judgement and best interests - substituted judgement in particular - and support for a combination of both or for a 'something else' option may reflect the complexity of proxy decisions in practice. This complexity was described as a complex weighing process of the proxy's substituted judgement, with their own preferences, and with the person's current preferences (Karlawish et al. 2001). In

contrast to the rigid tripartite bioethical hierarchy of proxy decision-making standards (known wishes, substituted judgement and best interests), described as having become ‘canonical’ in the bioethics texts and professional codes (Sugarman and Sulmasy 2010), a picture emerges from the data of complex multifaceted decisions that often involve a weighing up of numerous factors. As one participant noted, in real life it is not a ‘narrow framework’ (Black et al. 2013).

Interplay between the dimensions of framing criteria and active elements

The four active elements (**Figure 2, B**) influence how proxy decisions are made by modifying the framing criteria used by the proxy, and in turn, how or when the elements are drawn upon is influenced by the criteria used. Active elements had a varying functional role. They were persistently involved as factors considered by the proxy, as indicators to the proxy for how they should frame the decision, and sometimes as justification for the decision itself, it varied by context, patient-proxy relationship, and the attitude of the proxy themselves.

Associations also exist between a number of elements. The nature of the relationship between the person and their proxy is one such element that operates in both substituted judgement and best interests approaches, and is also linked to the ‘knowing the person’ element. The relationship provides the proxy’s authority to make decisions on behalf of adults lacking capacity (Buchanan and Brock 1989) by enabling them to provide a substituted judgement, but the relationship can also enable to the proxy to be best placed to determine what is in the best interests of the person. The closeness of the relationship is the mechanism by which the proxy knows the person’s wishes and preferences, and is also the reason they are chosen by the person to represent them as proxy (Berger et al. 2005; Sachs et al. 1994).

By contrast, the accuracy element appears to only be relevant when substituted judgement is utilised by the proxy where, unlike in best interest approaches, there could be considered a 'correct answer' to match. Studies which explored the accuracy of a proxy's substituted judgement generally demonstrated moderate levels of accuracy or agreement between patients and their proxies. As a result, some authors noted that the variable predictive accuracy of proxy decision-makers raised questions about the ethics and validity of proxy decision-making (Bryant et al. 2013; Coppolino and Ackerson 2001), which threatened the ethical principle of autonomy for the patient (Newman et al. 2012). However, such studies have important limitations and methodological flaws (Johansson et al. 2008), including that these studies are based on the assumption that there is similarity in decision-making patterns in hypothetical and actual treatment situations (Kohn 2015). Despite the use of the patient's own 'decision' as the gold standard, the patient is merely expressing a prediction (a preference or disposition (Egonsson 2010) rather than a consent decision, and in reality, proxies are being required to 'match a guess'.

Individuals also reported granting leeway or a margin of flexibility to their proxy, even when an advanced directive was in place. This appears to reflect their understanding that these are future decisions, which means that factors and information will be involved that are not currently known, and therefore the decision outcome cannot be pre-determined. Leeway appears to be influenced by perceived risks and benefits. Factors such as leeway and knowledge of relevant advance directives may also be part of 'knowing the person' that a proxy would incorporate into their substituted judgement. Knowledge of the person's altruistic tendencies may function in a similar role, but may also be affected by the proxy's own altruism, linked to selfish reasons or otherwise (Dawkins 2006).

One element - the risks and benefits of participating and the nature and invasiveness of the study procedures - was identified as a characteristic that operated to influence proxy decision-making in a number of different roles. It determined whether a substituted judgement or best interest determination was made by proxies, where if the burden was considered to be high then a substituted judgement was rejected, and best interests was used by some proxies (Burns et al. 2017) although not by all (Dunn et al. 2013). It also served as a justifying reason for the decision itself, where it was the 'right' decision if the person could gain benefit from participating (Aayalon et al. 2009).

The attitudes of the proxy towards research involving people without capacity, and in particular their willingness to participate in research themselves also operated at a number of levels and directions. The studies reported moderate to high levels of support for involving people who lack capacity in research, and acceptability of proxy consent models, although this too appeared to vary by perception of study risk and invasiveness of study procedures. Proxies who were willing to participate themselves were sometimes more likely to enrol the other person in two critical care studies (Clarridge et al. 2015; Lim et al. 2015), although this was not observed in other studies in dementia (Sachs et al. 1994; Kim et al. 2013) which supports the contextualised nature of decision-making. Proxies' decisions for the others generally reflected what they would want done for themselves, suggesting that rather than the proxy 'standing in the shoes' of the patient, the proxy decides as though the patient were in their (the proxy's) own shoes (Muncie et al. 1997). This may be because, when faced with uncertainty about what to decide when a person's wishes were not clear, the proxies considered themselves to be 'the reasonable person', and

therefore decisions they would make for themselves should be applicable to the other person (Muncie et al. 1997).

Gaps in the empirical evidence

The review identified important gaps in the empirical literature. The included studies were predominantly conducted in North America, for example no studies from the UK, or Africa were found, only one from Europe and Asia respectively. None of the included studies involved people who had experienced head injury, mental illness, or those requiring palliative care, which make up a proportion of the population with impaired capacity. Additionally, proxies for individuals who have never possessed decision-making capacity, such as people with profound intellectual or developmental disabilities, were not included in any of the studies. Many of the studies involved hypothetical scenarios, and in some studies participants had little or no experience of making actual decisions about research or proxy decision-making. This may affect the generalisability of the findings from the included studies.

No studies reported the experiences of researchers or health or social care professionals acting as proxy decisions-maker by virtue of their professional role where no personal proxy was available – although this may reflect the legal position in the jurisdictions the studies were conducted in. The study which included data on support for, or comfort with, professional or clinician involvement in decision-making showed low levels of support for professional decision-makers (Del Giudice et al. 2009), although this is authorised in a number of jurisdictions (De Martino et al. 2017, Mental Capacity Act 2005, Medicines for Human Use (Clinical Trials) Regulations 2004).

Strengths and limitations

This is the first study to systematically review data from empirical studies exploring proxy decision-making for research. Pragmatic search strategies were used in order to include a wide range of populations and methodologies to provide a rich and contextualised account. A framework synthesis approach has enabled a novel conceptual framework to be developed which is informed by the empirical data, and addresses the complexity of proxy decision-making.

The shortcomings of empirical research in medical ethics have been debated, including that a lack of normative analysis means that the empirical studies remain on a descriptive level (Salloch et al. 2012). Attempting to draw (meaningful) normative conclusions from empirical studies has been widely criticised (Ives, Dunn and Cribb 2017, 5). Normative analysis of the findings from this review are considered to be beyond the scope of this paper, however this paper does enable a broad view of the empirical literature in a form which is suitable for further normative analysis.

Limitations of the studies reviewed include that the difficulty with search filters' sensitivity and specificity in identifying 'ethical' issues may have resulted in relevant studies not being included in the review. The restricted populations and settings of the included studies may limit the transferability of the studies to other populations and jurisdictions. Patients who were included were, necessarily, those with less severe dementia, or survivors of critical illnesses who had regained decision-making capacity.

Extracted data were not coded independently as this review used an interpretive, iterative approach and we were therefore not coding data for reliability. The review team established the validity of coding through discussion and achieving consensus between three researchers during the iterative coding process.

Methodological flaws limit the generalisability of some studies that explored the accuracy of proxy predictions, and caution must be used when interpreting the findings and drawing conclusions about the ethical validity of proxy decision-making as a result. The complexity of proxy decision-making for research, and the myriad of ethical issues involved, are problematic to research using empirical methods. Quantitative methods using survey and questionnaire tools do not sufficiently capture the depth of the proxy experience, nor the views of patients and members of the public.

Studies that explored the framing criteria for decision-making commonly asked proxies and patients to state whether they supported, or used, a substituted judgement or a best interests approach, or both. These terms were not necessarily explained to participants, nor did authors interpret participants' responses consistently, and studies may have been affected by participants providing socially acceptable responses.

Conclusions

This review has sought to systematically review the empirical research on proxy decision-making for research involving adults who lack capacity, using a framework synthesis approach. Decision-making on behalf of a person who lacks capacity is

complex, ethically challenging, and highly contextualised and multifactorial in nature. The uncertainty about how decisions ought to be made by proxies, the weight of making a decision on behalf of another person, whilst balancing any potential risks or benefits, is burdensome for proxies.

The accounts of proxy decision-making given in normative ethical literature (and required by ethical frameworks) are not clearly or unequivocally supported by the empirical data on decision-making in practice, nor do they definitively reflect the views and preferences of those who are likely to require proxy decision-making. The findings from this review challenge the accepted reductive approach to proxy decision-making. It emphasises the differences between the standard interpretation of substituted judgement where the proxy is required to replicate the decision the person would have made, if they had capacity to do so, which studies using the 'gold standard and diagnostic test for accuracy' attempt to test empirically, and the reported experiences of proxies. Proxies tell a story of balancing a number of factors during the decision-making process, which seeks to honour the person's wishes while assessing the risks and benefits for the patient.

The studies suggest that the relationship between the patient and the proxy has a fundamental role. The relationship is the justifying reason for being chosen or acting as a proxy, it provides the proxy's authority to act on the person's behalf, and influences the factors incorporated into the decision-making process through their knowledge of the person.

The empirically informed framework for proxy decision-making for research proposed here represents an initial attempt to take account of the contextual use of substituted judgement and best interests approaches, and the balancing of the active elements

in the decision-making identified in this systematic review. This review indicates that this may more accurately reflect both decision-making in practice as reported by participants in the studies reviewed, and the reasons for having someone who knows the person well act as their proxy. Further work to describe and develop the framework, together with empirically testing the framework with those involved in proxy decisions about research participation, may be more helpful than seeking ways to improve proxies' ability to 'match a guess' in a world of counterfactual wishes and hypothetical scenarios.

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Competing interests

None.

Author's contributions

This study forms part of a Doctoral Research Fellowship held by VS, and supervised by FW, KH, RG, MS. VS, FW, KH, RG, MS conceived the study. VS, FW and KH devised the search strategy in conjunction with an Information Specialist. VS conducted the searches. VS, AJ and FW screened potentially relevant studies. VS

and AJ independently extracted data from the included studies. All authors were involved with interpretation and synthesis of the data, and development of the conceptual framework. VS drafted the manuscript, all authors critically revised the manuscript, and subsequent revisions. The submitted version was approved by all authors.

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Appendix 1 Search strategy

Initial searches were developed in December 2016 using MEDLINE. A literature review of the analytical/philosophical literature helped to develop the initial conceptual framework and inform the initial search strategy. Subsequent searches were developed with attention to the conceptual framework and terms used in the literature. Final searches were conducted in January and February 2017.

Electronic resources

- Ovid MEDLINE <1946 to January Week 3 2017>
- EMBASE <1996- 2017 January 03>
- PsychINFO <1806 – present>
- CINAHL plus with full text <1986-present>
- BNI <1985-present>
- SCOPUS <1966-present>
- Web of Science <1900-present>
- EUROETHICS

Studies were limited to those in the English language, the search was not limited by date. Supplementary searches were conducted including citation tracking, reference lists of included papers, and electronic table of contents (eTOC) of key journals for the last two years.

Example search strategy

Ovid MEDLINE <1946 to January Week 3 2017>

1. exp Proxy/
2. proxies.tw.
3. exp Informed Consent/
4. exp Third-Party Consent/
5. (consent adj3 (informed or proxy or proxies or surrogate*)).tw.
6. (proxy* adj3 (consent or choice* or decision* or decide or choose or prefer or permission or view*)).tw.
7. (proxies adj3 (consent or choice* or decision* or decide or choose or prefer or permission or view*)).tw.
8. (surrogate* adj3 (consent or choice* or decision* or decide or choose or prefer or permission or view* or preference*)).tw.
9. (informed consent adj3 (proxy or proxies or surrogate*)).tw.
10. (substitute* adj3 (consent or choice* or decision* or decide or choose or prefer or permission or view)).tw.
11. (principle* adj2 ethic*).tw.

12. (accuracy adj4 (proxy or proxies or surrogate* or decision)).tw.
13. substituted judgement*.tw.
14. best interest*.tw.
15. comfort.tw.
16. (trial* or study or studies or research).tw.
17. (empirical* adj3 (study or studies)).tw.
18. (philosoph* adj3 (study or studies)).tw.
19. exp "Surveys and Questionnaires"/
20. (("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)).ti,ab.
21. or/11-15
22. or/16-20
23. or/1-10
24. 21 and 22 and 23