NIA IMPACT COLLABORATORY
TRANSFORMING DEMENTIA CARE

Ethical challenges with pragmatic RCTs: General issues and special considerations in dementia

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Housekeeping

- All participants will be muted
- Enter **all questions** in the Zoom **Q&A** or **chat box** and send to All Panelists and Attendees
- Moderator will review questions from chat box and ask them at the end
- Want to continue the discussion? Look for the associated podcast released about 2 weeks after Grand Rounds.
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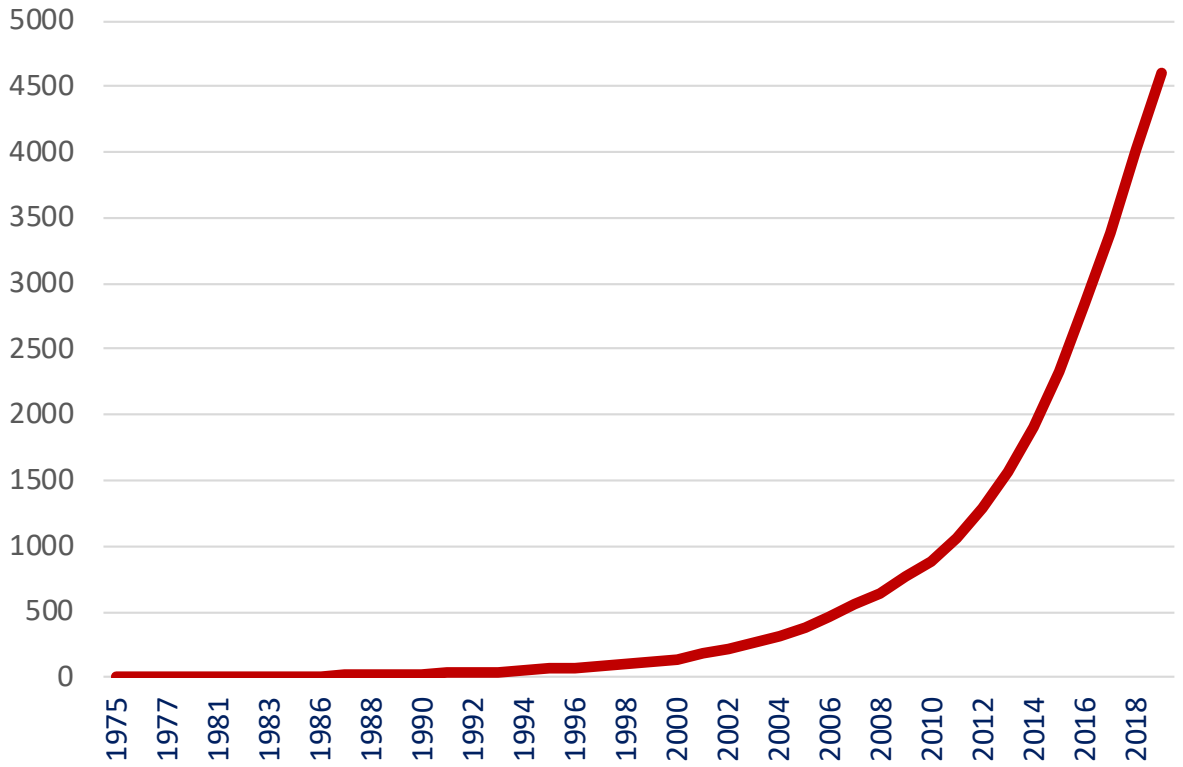
Objectives

1. Discuss key features of pragmatic RCTs and the contexts in which ethical issues arise
2. Outline a program of research to develop principle-based guidance for the ethical design and conduct of pragmatic RCTs
3. Describe key ethical issues raised by pragmatic RCTs and which may be particularly salient to the ADRD context
4. Describe the challenges of identifying a sample of pragmatic RCTs from the literature
5. Describe the landscape of key ethical issues in published pragmatic RCTs in ADRD

The increasing popularity of pragmatic trials

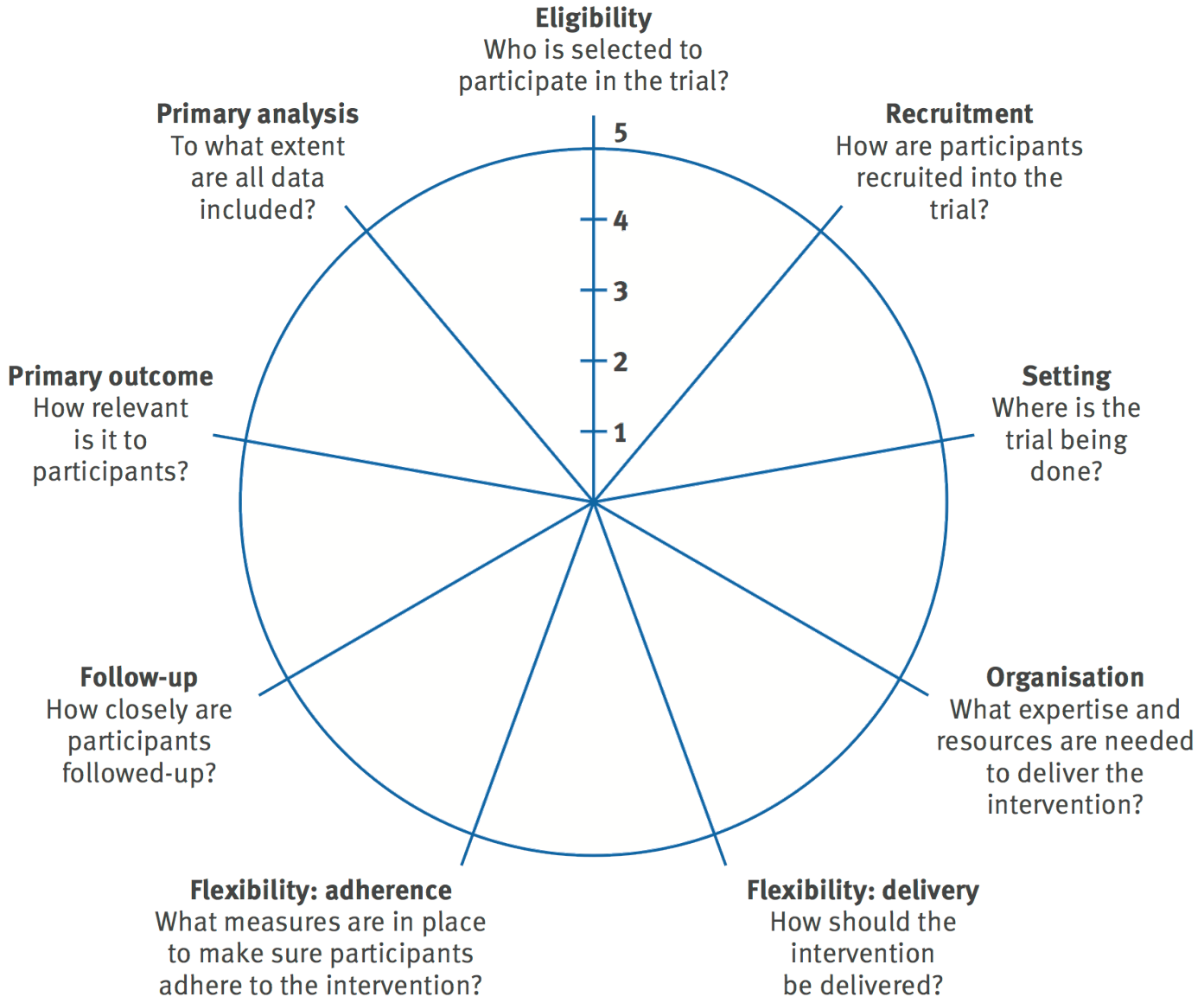
- **Pragmatic RCTs** *are intended to have their results be applicable to clinical or health policy decisions* and should thus mimic as closely as possible the users, settings and circumstances in which it is thought the interventions under evaluation will be used



Cumulative number of publications in PubMed using the words "pragmatic" and "trial" in the title or abstract (searched 12 September 2019)

Taljaard, M., S. McDonald, S. G. Nicholls, K. Carroll, S. P. Hey, J. M. Grimshaw, D. A. Fergusson, M. Zwarenstein and J. E. McKenzie (2020). "A search filter to identify pragmatic trials in MEDLINE was highly specific but lacked sensitivity." Journal of Clinical Epidemiology 124: 75-84.

- **Tools such as PRECIS-2** have been designed to assist *investigators prospectively* think about the degree of pragmatism in *their* trial.



Loudon K, et al The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ.* 2015;350:h2147

A principle-based approach to ethics guidance

Taljaard et al. Trials (2018) 19:525
https://doi.org/10.1186/s13063-018-2895-x

Trials

STUDY PROTOCOL Open Access

Developing a framework for the ethical design and conduct of pragmatic trials in healthcare: a mixed methods research protocol

Monica Taljaard[1,2*], Charles Weijer[3], Jeremy M. Grimshaw[2,4,5], Adnan Ali[6], Jamie C. Brehaut[2,4], Marion K. Campbell[7], Kelly Carroll[4], Sarah Edwards[8], Sandra Eldridge[9], Christopher B. Forrest[10], Bruno Giraudeau[11,12], Cory E. Goldstein[3], Ian D. Graham[2,4], Karla Hemming[13], Spencer Phillips Hey[14,15], Austin R. Horn[3], Vipul Jairath[16,17], Terry P. Klassen[18], Alex John London[19], Susan Marlin[20], John C. Marshall[21], Lauralyn McIntyre[2,4,22], Joanne E. McKenzie[23], Stuart G. Nicholls[1], P. Alison Paprica[24], Merrick Zwarenstein[25] and Dean A. Fergusson[1,2,5]

- To date much of the research has been:
  - Limited to a few specific topics (e.g. consent)
  - Based on vignettes or hypothetical in nature
  - Restricted to few jurisdictions (e.g. US)
- The overarching goal of our project is to develop principle-based guidance for the ethical design and conduct of pragmatic trials
  - Empirical analyses: literature review(s), primary data collection
  - Conduct ethical analyses
  - Consensus process

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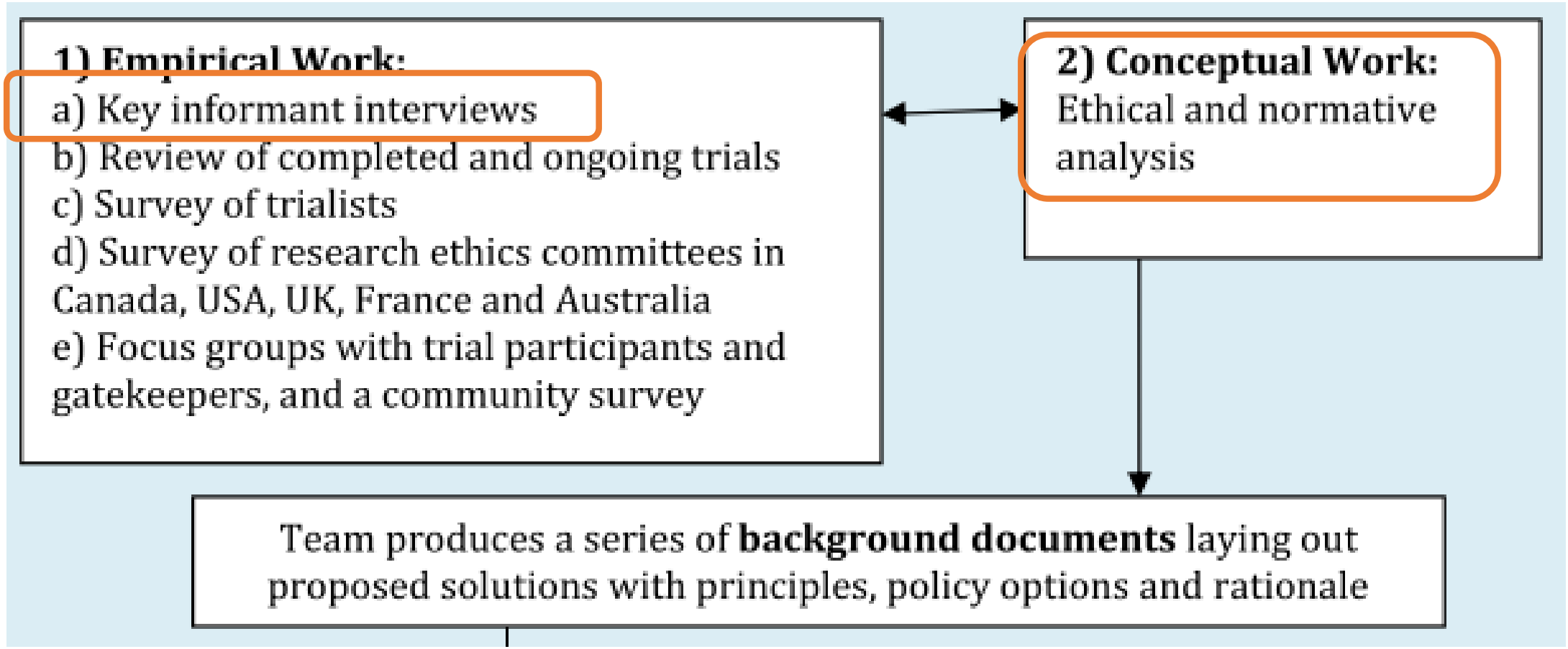
Ethical challenges in pragmatic RCTs



Taljaard, M., C. Weijer, J. M. Grimshaw, A. Ali, J. C. Brehaut, M. K. Campbell, K. Carroll, S. Edwards, S. Eldridge, C. B. Forrest, B. Giraudeau, C. E. Goldstein, I. D. Graham, K. Hemming, S. P. Hey, A. R. Horn, V. Jairath, T. P. Klassen, A. J. London, S. Marlin, J. C. Marshall, L. McIntyre, J. E. McKenzie, S. G. Nicholls, P. Alison Paprica, M. Zwarenstein and D. A. Fergusson (2018). "Developing a framework for the ethical design and conduct of pragmatic trials in healthcare: a mixed methods research protocol." Trials 19(1): 525.

Goldstein *et al. BMC Medical Ethics* (2018) 19:14
https://doi.org/10.1186/s12910-018-0253-x

BMC Medical Ethics

RESEARCH ARTICLE Open Access

Ethical issues in pragmatic randomized controlled trials: a review of the recent literature identifies gaps in ethical argumentation

Cory E. Goldstein[1*], Charles Weijer[1], Jamie C. Brehaut[2], Dean A. Fergusson[2], Jeremy M. Grimshaw[2], Austin R. Horn[1] and Monica Taljaard[2]

Nicholls *et al. Trials* (2019) 20:765
https://doi.org/10.1186/s13063-019-3899-x

Trials

RESEARCH Open Access

The ethical challenges raised in the design and conduct of pragmatic trials: an interview study with key stakeholders

Stuart G. Nicholls[1*], Kelly Carroll[1], Merrick Zwarenstein[2], Jamie C. Brehaut[1,3], Charles Weijer[4], Spencer P. Hey[5], Cory E. Goldstein[4], Ian D. Graham[1,3], Jeremy M. Grimshaw[1,3,6], Joanne E. McKenzie[7], Dean A. Fergusson[1,3,6], Monica Taljaard[1,3], on behalf of the Ethics of Pragmatic Trials project

Key ethical issues

Ethical and Regulatory Issues for Embedded Pragmatic Trials Involving People Living with Dementia

Emily A. Largent, JD, PhD, RN, Spencer Phillips Hey, PhD,† Kristin Harkins, MPH,‡ Allison K. Hoffman, JD,§ Steven Joffe, MD, MPH,* Julie C. Lima, PhD, MPH,¶‖ Alex John London, PhD,** and Jason Karlawish, MD*‡††*

Achieving Health Equity in Embedded Pragmatic Trials for People Living with Dementia and Their Family Caregivers

Ana R. Quiñones, PhD,† Susan L. Mitchell, MD,‡§ Jonathan D. Jackson, PhD,¶ María P. Aranda, PhD,‖ Peggye Dilworth-Anderson, PhD,** Ellen P. McCarthy, PhD,‡§ and Ladson Hinton, MD††*

Key ethical issues

- What are the ethically important distinction(s) between research, clinical practice and quality improvement in pragmatic trials (if any)?
  - What criteria should be used to determine the type of oversight and regulation necessary for a pragmatic RCT? How would regulatory oversight differ depending on the conclusion?
- When are alterations and waivers of traditional informed consent appropriate in pragmatic RCTs? For what is consent required?
  - For PLWD, how is capacity considered or evaluated? When are substitute decision-makers required? What role for assent, even if full consent is waived? What role for notification?
- Who are the stakeholders who have roles or responsibilities in relation to the trial (and how do we determine the individuals or groups who have roles)? What are their duties or responsibilities within the trial?
  - E.g. nursing home staff, owners, managers

Key ethical issues

- Who are the individuals or groups affected by the trial (and how do we determine who have legitimate claims on those conducting the trial)?
  - How should we think about dyads of PLWD and their caregiver? Are there responsibilities to caregivers who may be directly impacted by the involvement of a dementia patient in an RCT, even if the caregiver is not a research participant?
  - What special protections should be in place, and for whom?
- What are the responsibilities of identified stakeholders with respect to equity of access to pragmatic RCTs for those who are eligible? How should these responsibilities be determined?
  - Are there systemic barriers based on circumstance rather than inclusion/exclusion criteria?

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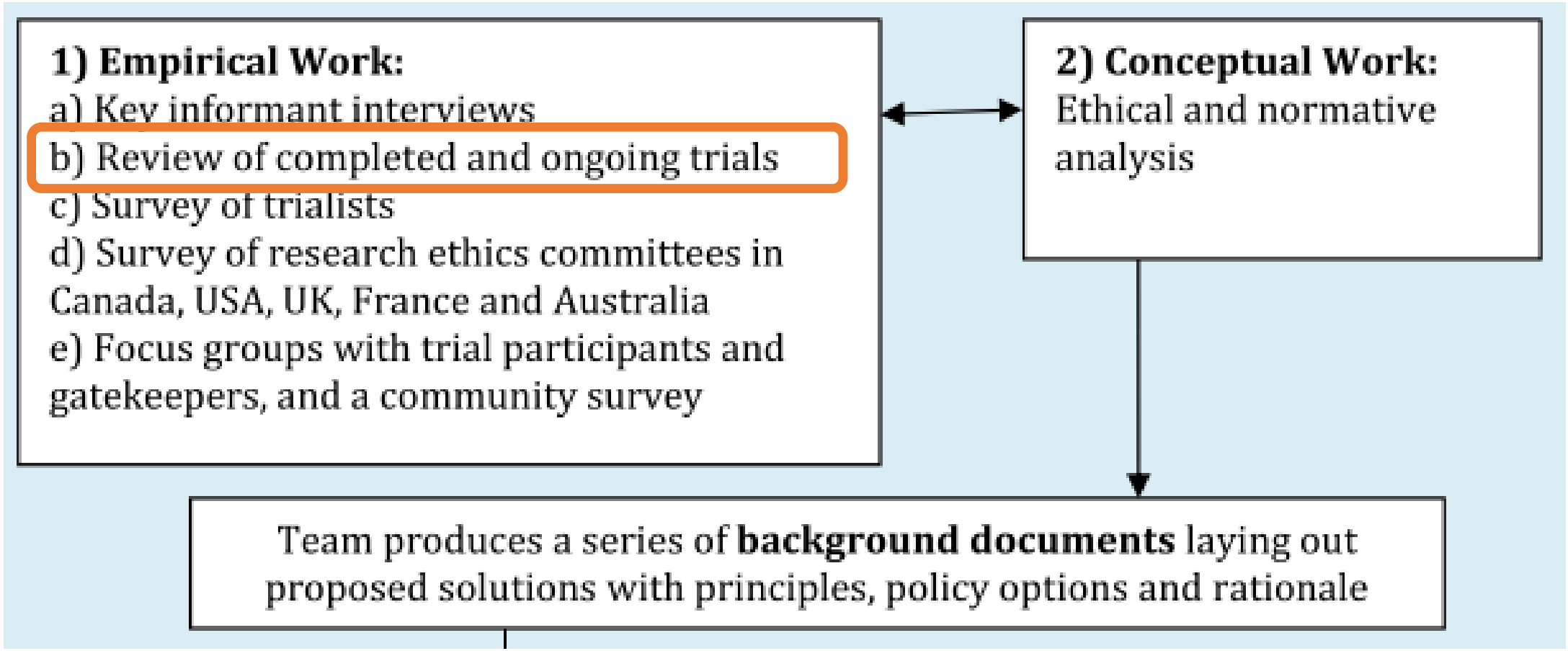
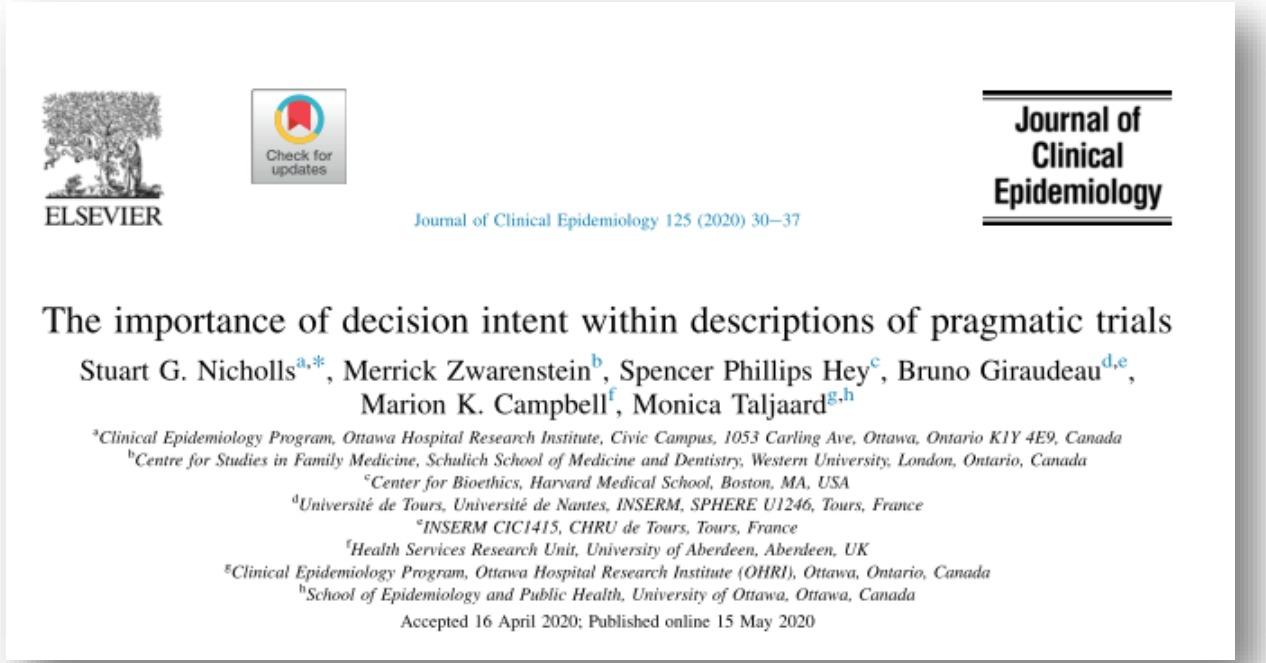
Identifying key ethical issues within published pragmatic RCTs



Taljaard, M., C. Weijer, J. M. Grimshaw, A. Ali, J. C. Brehaut, M. K. Campbell, K. Carroll, S. Edwards, S. Eldridge, C. B. Forrest, B. Giraudeau, C. E. Goldstein, I. D. Graham, K. Hemming, S. P. Hey, A. R. Horn, V. Jairath, T. P. Klassen, A. J. London, S. Marlin, J. C. Marshall, L. McIntyre, J. E. McKenzie, S. G. Nicholls, P. Alison Paprica, M. Zwarenstein and D. A. Fergusson (2018). "Developing a framework for the ethical design and conduct of pragmatic trials in healthcare: a mixed methods research protocol." Trials 19(1): 525.

How do we identify a published pragmatic RCT?

- Existing reviews largely relied on self-identification as a pragmatic RCT - no reporting guidelines require pragmatic trials to be labelled as such
- No single defining characteristic of a pragmatic RCTs
- Retrospective analysis using PRECIS-2?
  - Designed for prospective use by investigators when developing their own trial
  - Subjective assessment for scoring
  - No agreed thresholds for scoring or dichotomisation (continuum)
  - Should all PRECIS-2 domains be weighted equally?
  - Limits of reporting
  - PRECIS-2 not designed for certain types of trial e.g. cluster RCTs



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Check for updates

Journal of Clinical Epidemiology 125 (2020) 30–37

Journal of Clinical Epidemiology

The importance of decision intent within descriptions of pragmatic trials

Stuart G. Nicholls[a,*], Merrick Zwarenstein[b], Spencer Phillips Hey[c], Bruno Giraudeau[d,e], Marion K. Campbell[f], Monica Taljaard[g,h]

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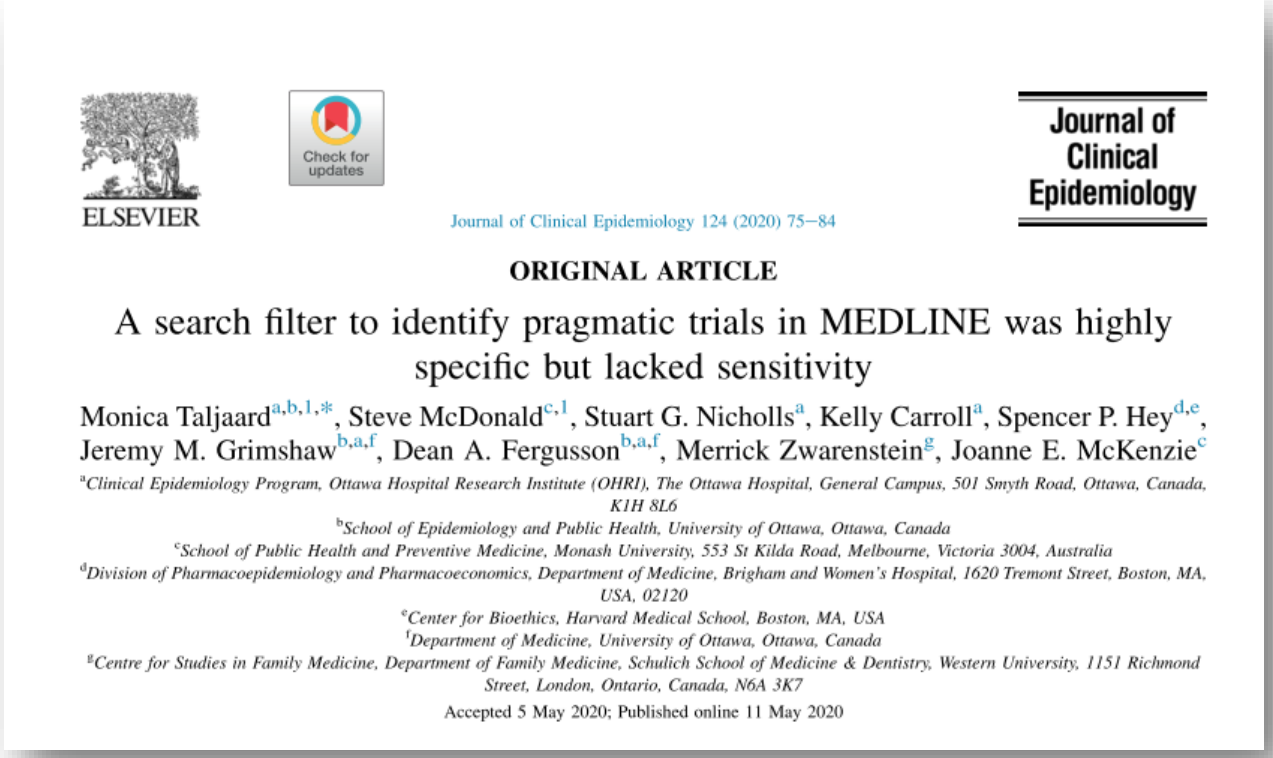
[b]Centre for Studies in Family Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada
[c]Center for Bioethics, Harvard Medical School, Boston, MA, USA
[d]Université de Tours, Université de Nantes, INSERM, SPHERE U1246, Tours, France
[e]INSERM CIC1415, CHRU de Tours, Tours, France
[f]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[g]Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), Ottawa, Ontario, Canada
[h]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada

Accepted 16 April 2020; Published online 15 May 2020

Identifying trials more likely to be pragmatic



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Journal of Clinical Epidemiology

Journal of Clinical Epidemiology 124 (2020) 75–84

ORIGINAL ARTICLE

A search filter to identify pragmatic trials in MEDLINE was highly specific but lacked sensitivity

Monica Taljaard[a,b,1,*], Steve McDonald[c,1], Stuart G. Nicholls[a], Kelly Carroll[a], Spencer P. Hey[d,e], Jeremy M. Grimshaw[b,a,f], Dean A. Fergusson[b,a,f], Merrick Zwarenstein[g], Joanne E. McKenzie[c]

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[b]*School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada*

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Accepted 5 May 2020; Published online 11 May 2020

- Key terms
  - Design terms: e.g. pragmatic, real world, unblinded, cluster, stepped wedge, phase IV
  - Attribute: e.g. primary care, comparative effectiveness, evidence based, patient oriented, usual care, registry based
- Search performance is superior to other ad hoc filters for pragmatic trials.
- Improved efficiency over the Cochrane search for randomized trials which retrieves 4.5 million records.

Landscape analysis

- Searched MEDLINE, Jan 1 2014 – 3 April 2019 (date of search)
- Excluded if:
  - Not an RCT
  - Pilot or feasibility study, or <100 participants
  - Not health or healthcare related
  - A non-primary trial report
  - Clearly not pragmatic, e.g. focused on isolating a biological impact of an intervention without a clear clinical implication, or trial that did not assess clinical outcomes.
- Yielded 4337 trial reports

Item	N (%)
Self-identification as "pragmatic":	
Anywhere (title, abstract or main text)	964 (22.2%)
In title or abstract	534 (12.3%)
In main text only (not in title or abstract))	430 (9.9%)
Identification as pragmatic by NLM	
Pragmatic Clinical Trial as Publication type*	268 (6.2%)
Pragmatic Clinical Trials as Topic*	22 (0.5%)

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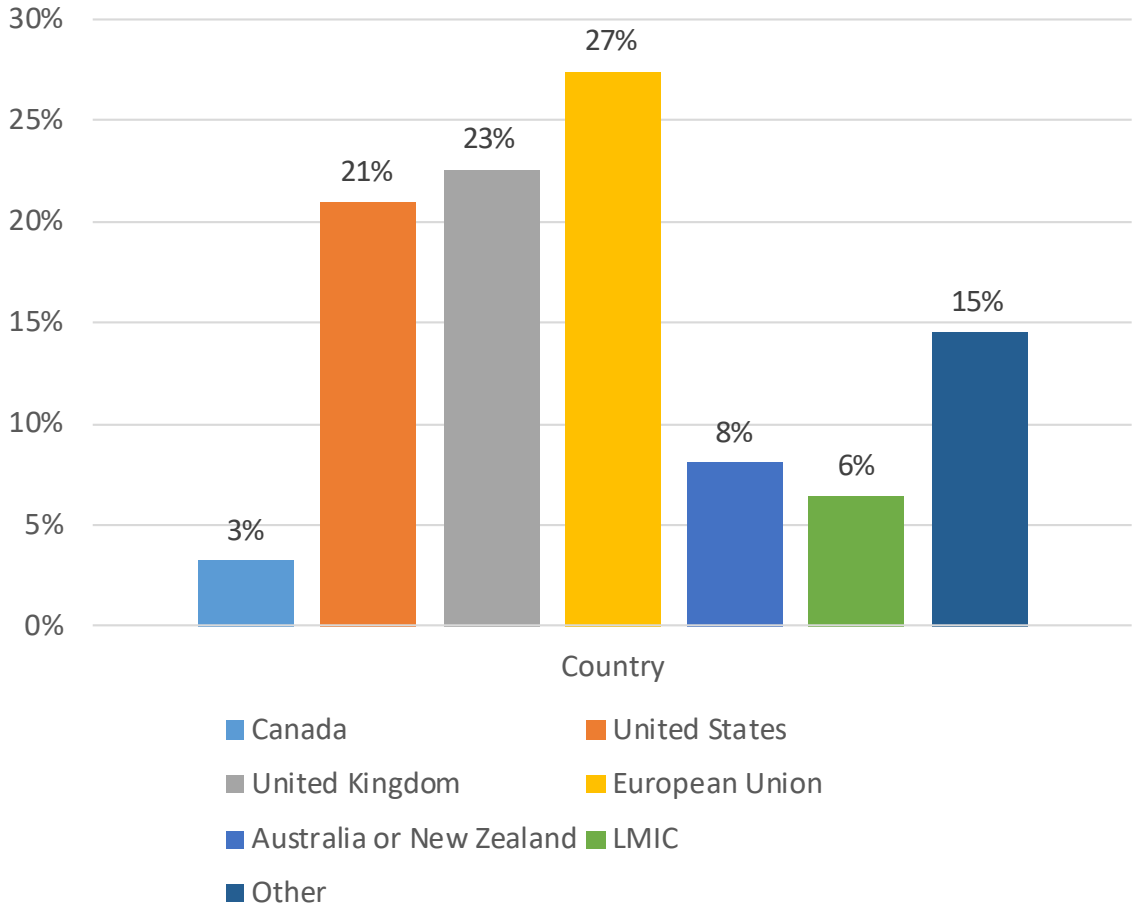
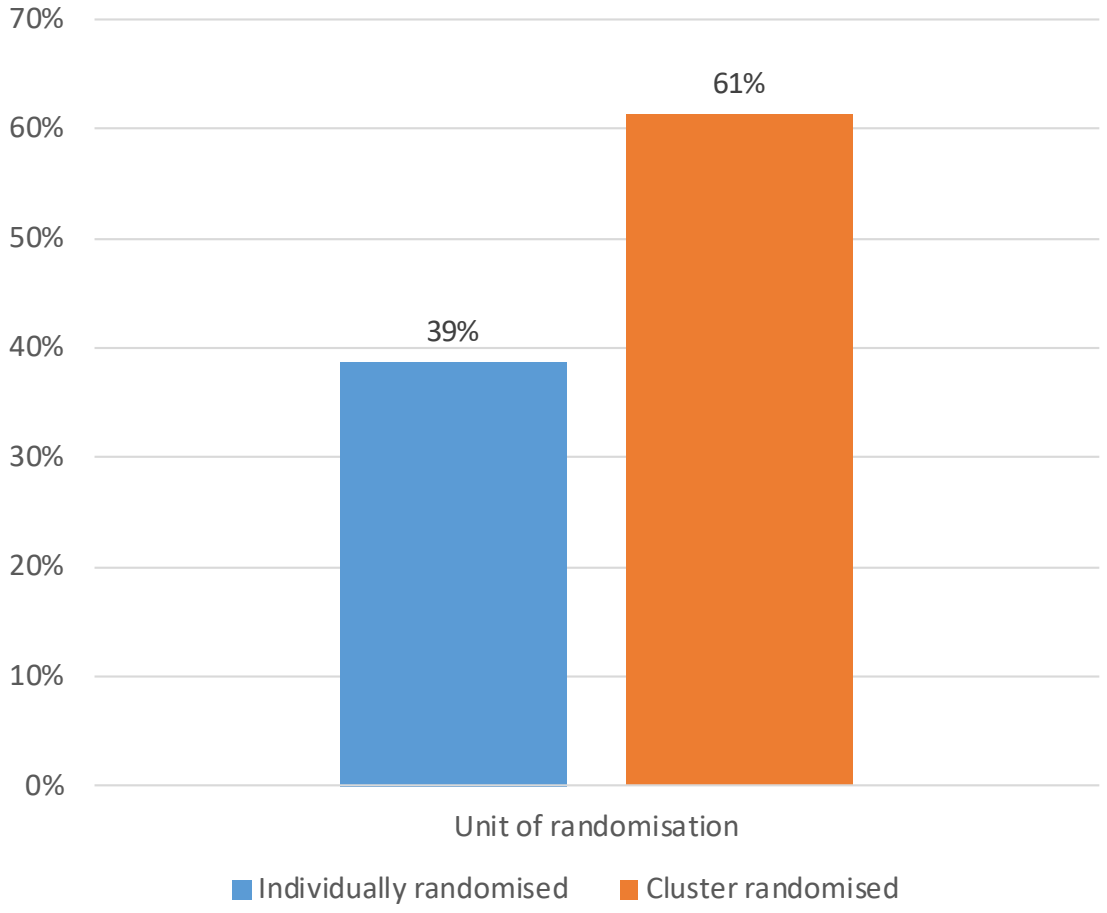
The reporting of ethical issues in pragmatic trials with PLWD

The reporting of ethical issues in pragmatic trials with PLWD

- From the larger sample of pragmatic RCTs (n=4337) identified trials that:
  - Specifically focused on (a) people living with dementia and/or their caregivers, or (b) a broader cohort of older adults which included a subgroup with dementia and conducted a stratified or subgroup analysis on that cohort
  - Applied a search filter from the Cochrane dementia and cognitive improvement group and MeSH terms to identify trials exclusively in those aged 65 and over
  - Final sample included N=62 RCTs
- Goal: To describe the reporting and ethical conduct of pragmatic trials in ADRD, with specific reference to previously identified ethical challenges
  - Focus on research-care distinction, human subject identification (including vulnerable groups and equity), consent approaches

Trial demographics (N=62)





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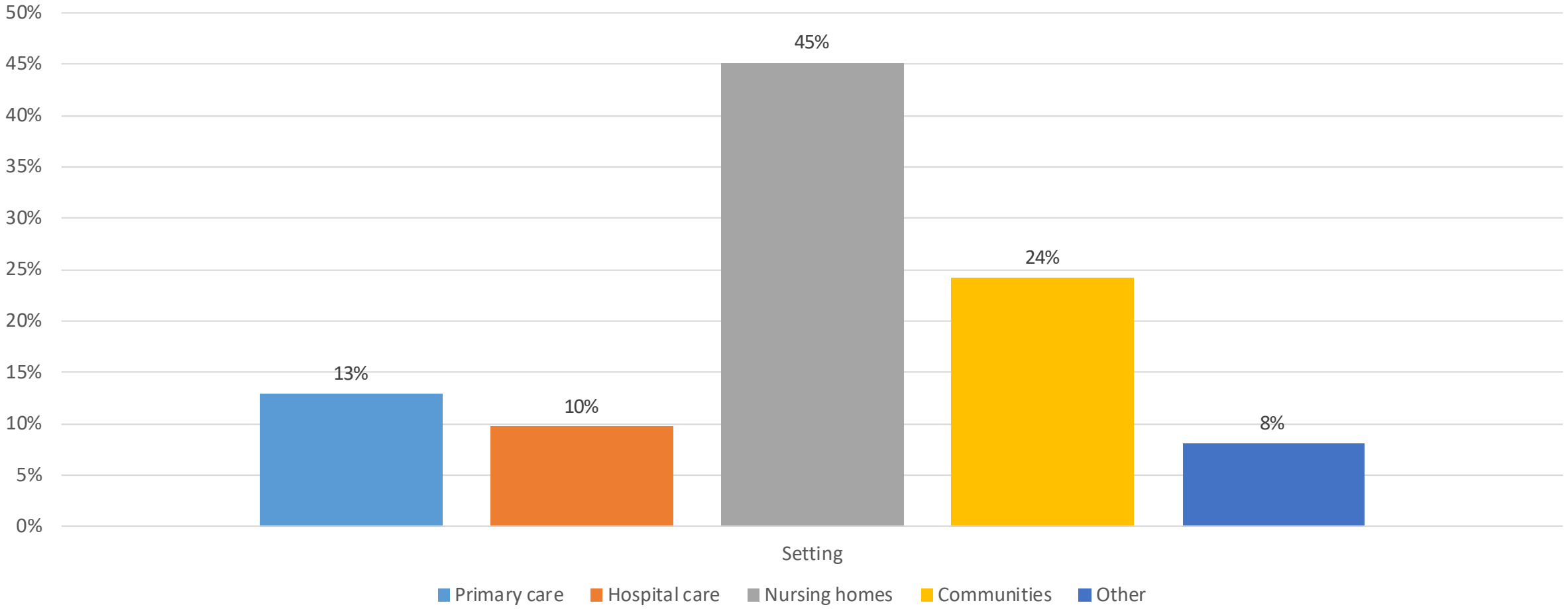
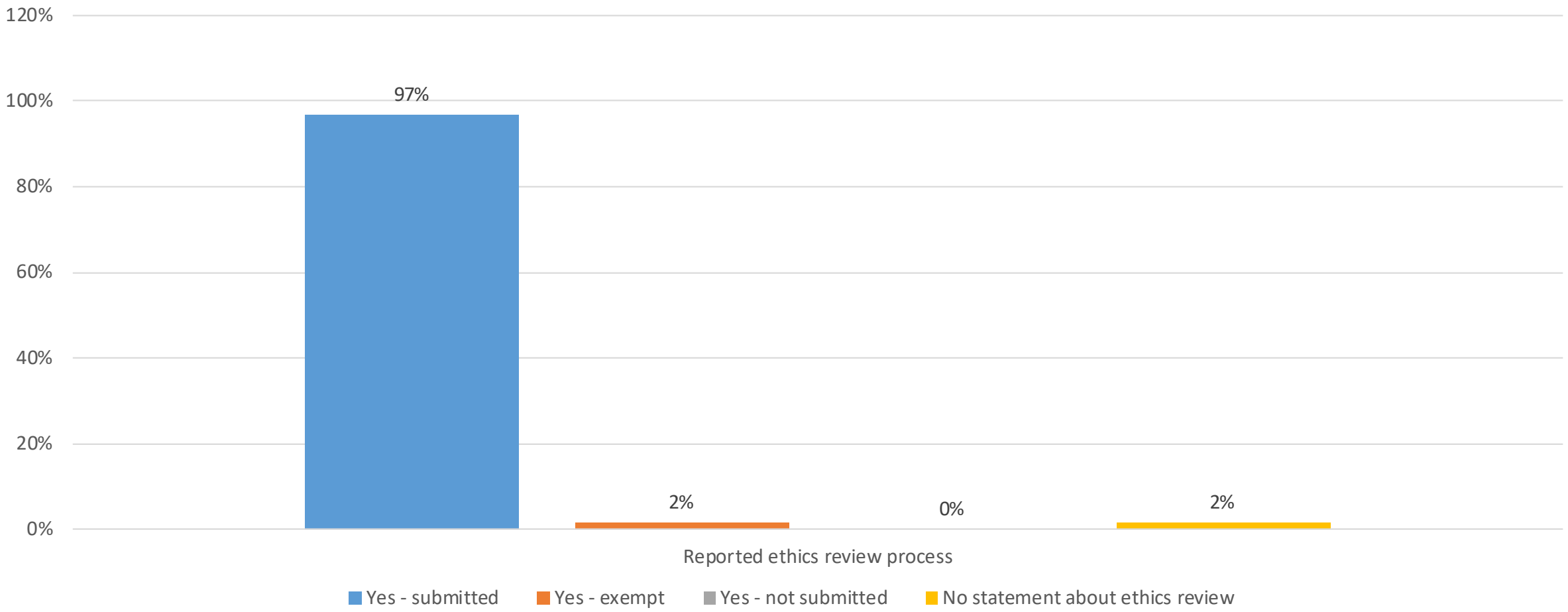
Trial setting (n=62)



Data extraction

Ethical issue	• Data extraction
Research/care distinction	• Did the manuscript report on ethics review? • If not submitted, why? If deemed exempt, why?
Subject identification/populations affected by the trial – including vulnerable groups and equity considerations	• Who was the research subject (patient with dementia, caregiver, healthcare professional, other)? • Explicit consideration of vulnerable groups and special protections • Explicit consideration of equity or differential effect of treatments
Informed consent, including waivers of consent and role of notification	• Was there any statement about individual level consent? • Was capacity to consent explicitly stated either as a requirement within the inclusion criteria or through the explicit exclusion of participants without capacity to consent? • For studies where the requirement for consent was not waived, was an assessment of capacity conducted with patients? (If yes, what tool or assessment measure was used?) • If consent was sought, for which aspects of the trial was consent sought? • What modes were used for obtaining consent (e.g. verbal, written etc)

Research/care distinction (n=62)



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Subject identification

OPEN ACCESS Freely available online

PLOS | MEDICINE

Guidelines and Guidance

The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

Charles Weijer[1,2,3]*, Jeremy M. Grimshaw[1,4,5], Martin P. Eccles[6], Andrew D. McRae[1,3,7], Angela White[1], Jamie C. Brehaut[4,8], Monica Taljaard[1,4,8], the Ottawa Ethics of Cluster Randomized Trials Consensus Group[¶]

1 Rotman Institute of Philosophy, Department of Philosophy, Western University, London, Ontario, Canada, **2** Department of Medicine, Western University, London, Ontario, Canada, **3** Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada, **4** Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, **5** Department of Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **6** Institute of Health and Society, Newcastle University, Newcastle upon Tyne, United Kingdom, **7** Division of Emergency Medicine, University of Calgary, Foothills Medical Centre, Calgary, Alberta, Canada, **8** Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada

A research participant can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual

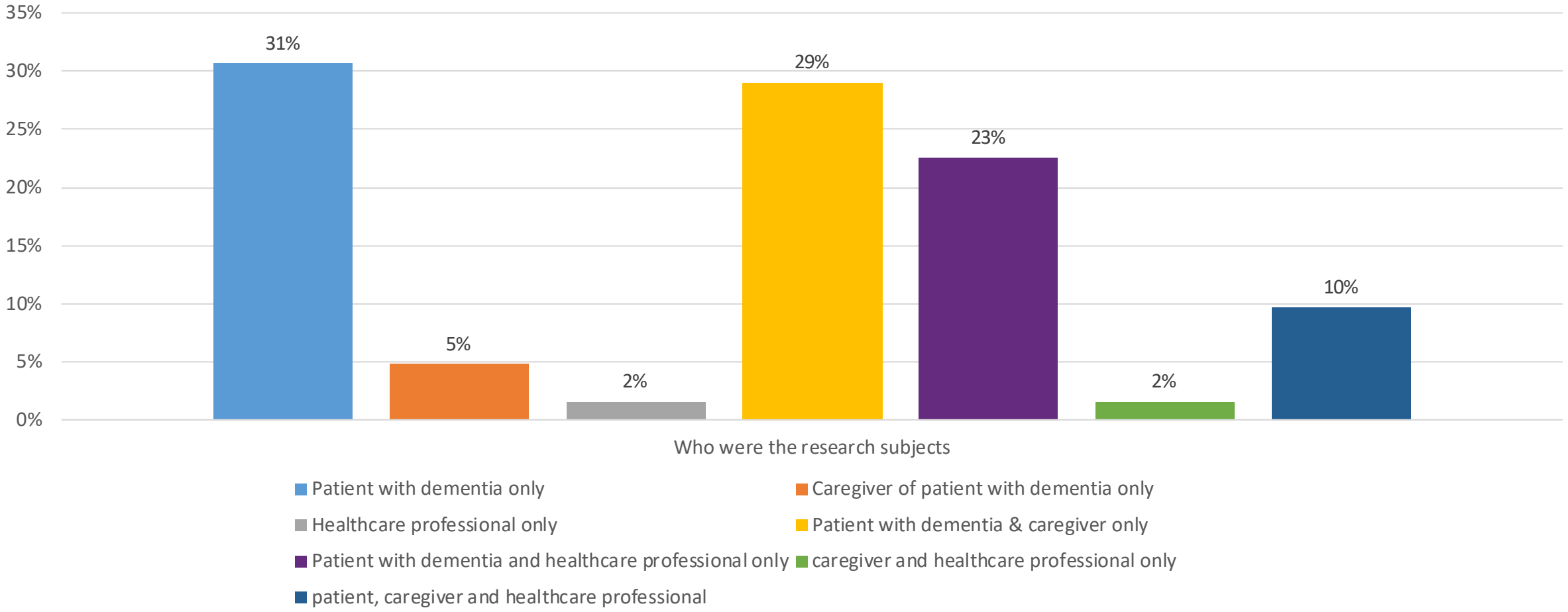
(1) who is the intended recipient of an experimental (or control) intervention; or

(2) who is the direct target of an experimental (or control) manipulation of his/her environment; or

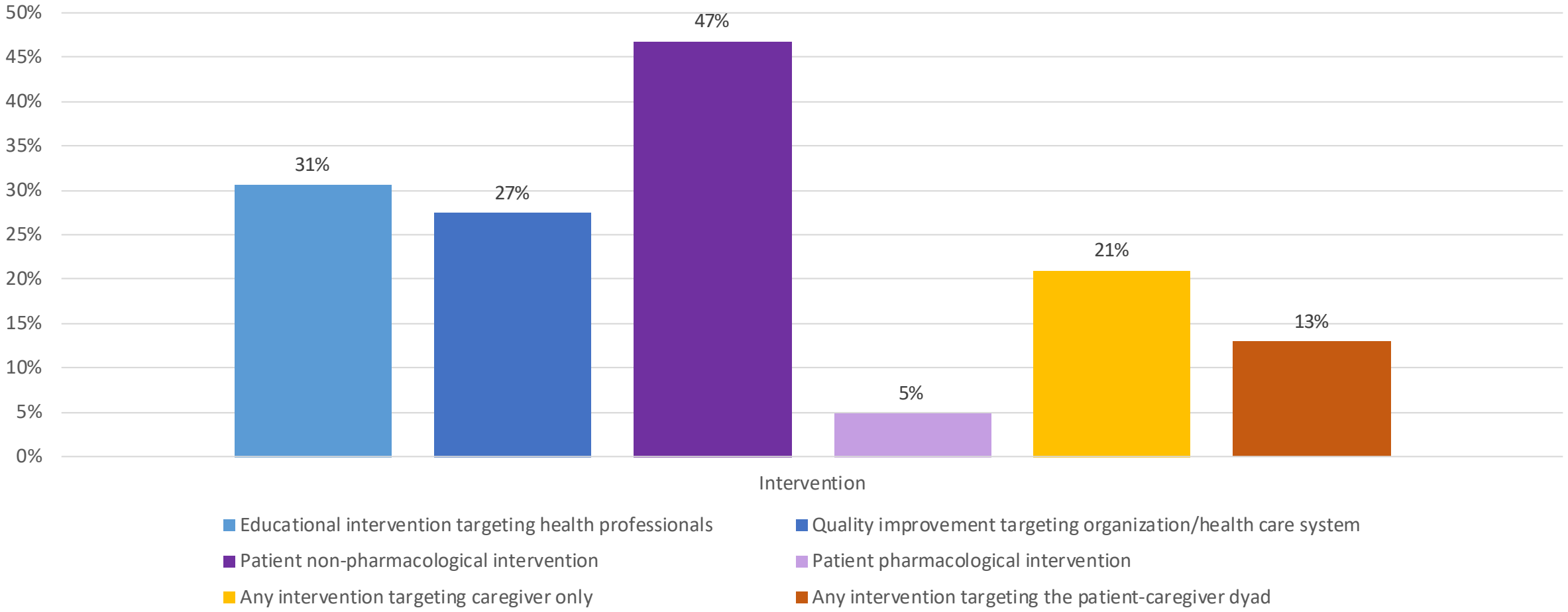
(3) with whom an investigator interacts for the purpose of collecting data about that individual; or

(4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual.”

Subject identification



Intervention (N=62)



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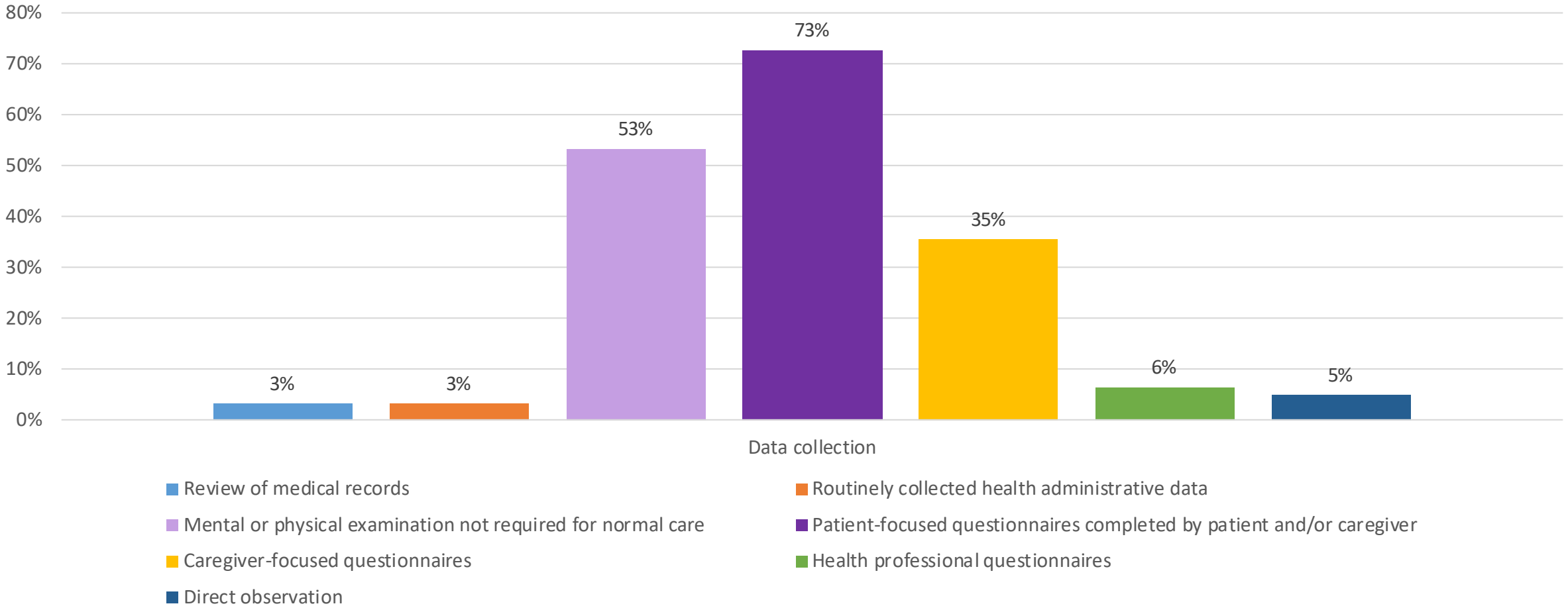
Multi-selections possible if multiple interventions

Data collection (N=62)



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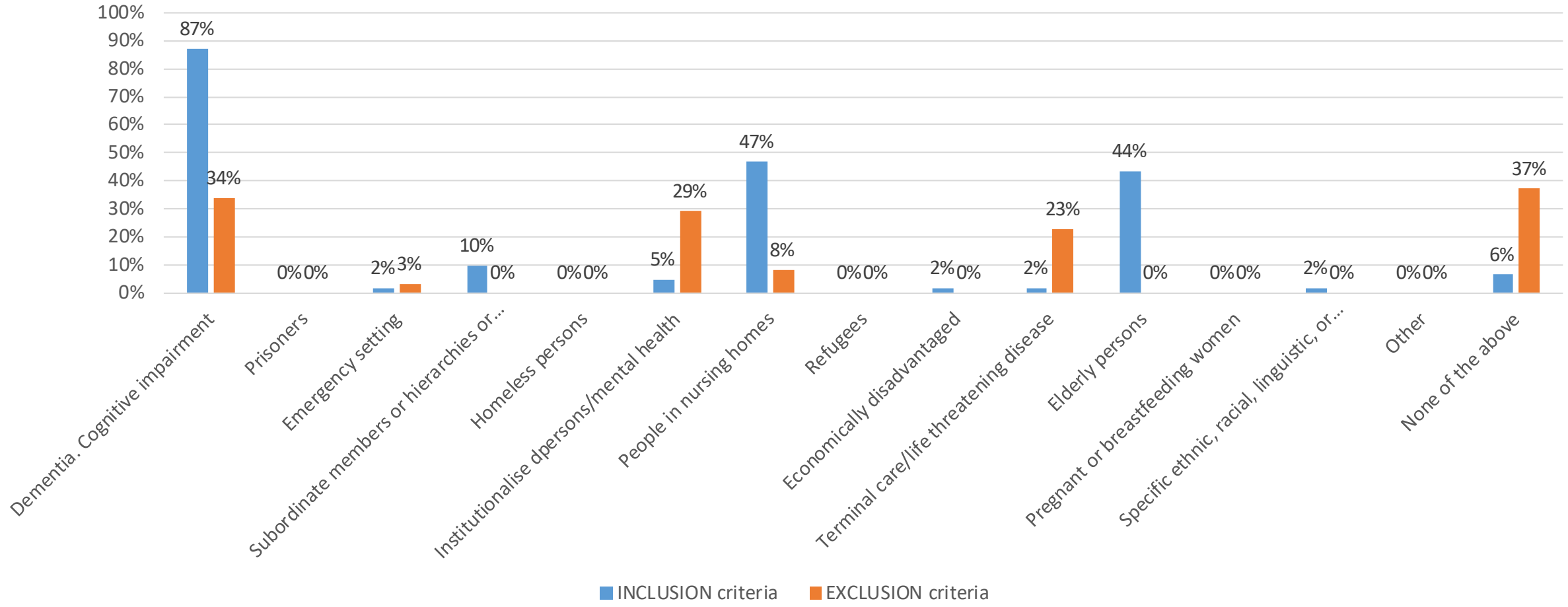
Multi-selections possible if multiple methods of data collection

Subject identification: vulnerable groups

1. Those with dementia, a cognitive impairment, or determined not to have capacity (Aus. National Statement)
2. Prisoners (CIOMS, ICH GCP, Aus. National Statement, TCPS2, Common Rule)
3. Patients in emergency setting (CIOMS, Clinical Trials Regulation, ICH GCP, TCPS2)
4. Subordinate members of hierarchies or relationships (for example, ***Nursing home staff*** or "medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police"(as per CIOMS)) (CIOMS, ICH GCP, Aus. National Statement)
5. Homeless persons (CIOMS, ICH GCP)
6. Institutionalised persons, or those with mental health problems beyond dementia (e.g. psychosis, learning disabilities etc.) (Clinical Trials Regulation, Aus. National Statement, TCPS2, UK Research Governance Framework, Belmont report)
7. Persons in nursing homes (CIOMS, ICH GCP)
8. Refugees or displaced persons (CIOMS, ICH GCP)
9. Economically disadvantaged persons (Belmont Report, Common Rule)
10. Patients in terminal care or who have life-threatening diseases (Australian National Statement, CIOMS, Belmont report)
11. Elderly persons (here defined as ≥ 65 years) (CIOMS, Clinical Trials Regulation, TCPS2)
12. Pregnant or breastfeeding women (Clinical Trials Regulation, Common Rule)
13. Specific ethnic, racial minority, linguistic, or ethnocultural groups (CIOMS, ICH GCP, TCPS2, Belmont Report)
14. Other (specify)

For more details see: Bracken-Roche, D., E. Bell, M. E. Macdonald and E. Racine (2017). "The concept of 'vulnerability' in research ethics: an in-depth analysis of policies and guidelines." Health Res Policy Syst 15(1): 8.

Vulnerable groups included/excluded*



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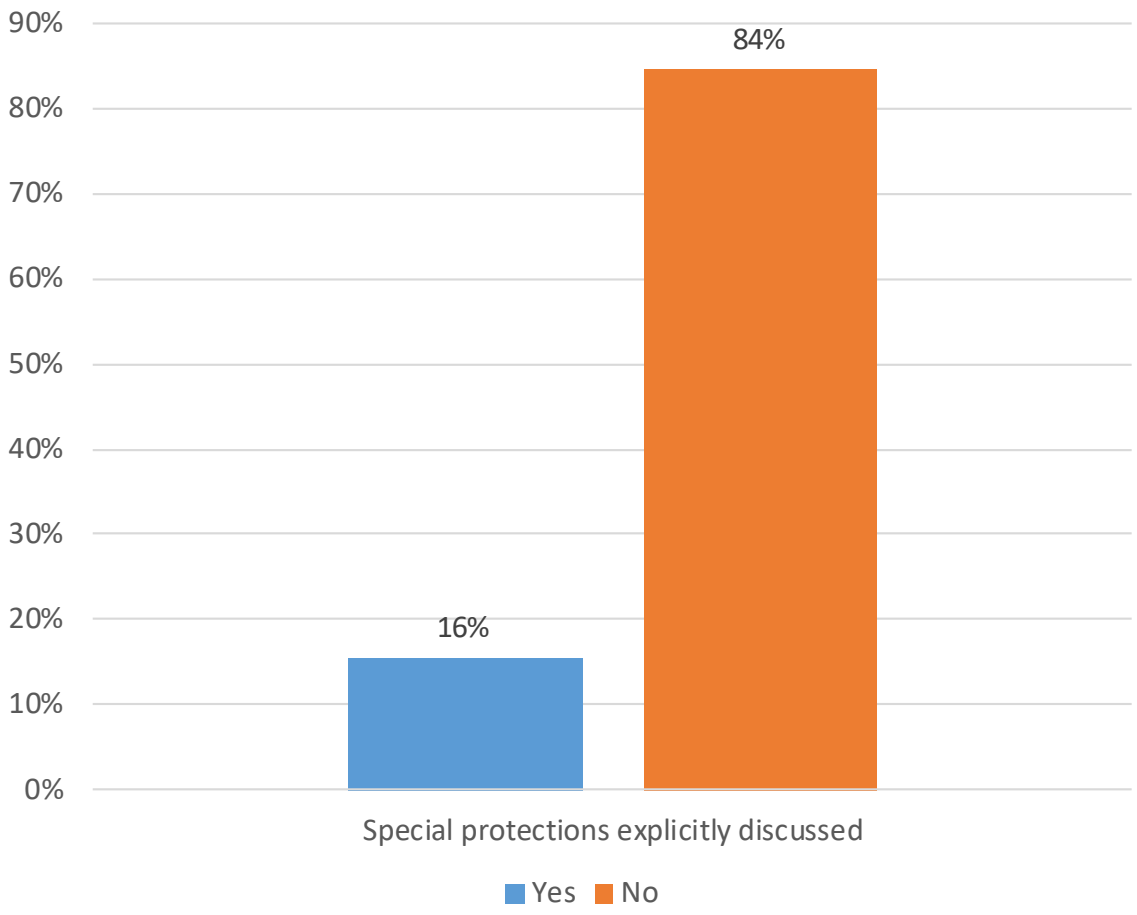
* Note: multiple selections possible

Special protections reported? (n=58)



- For example,
  - "Time was also taken within supervision to highlight the importance of behaving ethically and safely in all aspects of clinical work, for example reflecting on maintaining clear boundaries clinically and how to practise safely when working alone in people's homes."
  - "Our study was not powered to find a significant change in abuse and for ethical reasons we made clinicians aware of clinically significant abusive behaviour in the control group; thus, abused carers in this group were often offered clinical and social support as well as monitoring of the behaviour and, if felt appropriate, adult protection measures were taken."

Equity: subgroup analysis (PROGRESS)

1. **P**lace of residence (e.g. rural vs urban, but also comparison of countries, regions or towns)
2. **R**ace/ethnicity/culture or language (e.g. comparisons by race, cultural norms, or language especially if it is a language that isn't the primary language of the jurisdiction where the trial is being conducted)
3. **O**ccupation (e.g. analysis of migrant workers, by employment status)
4. **G**ender/Sex (e.g. comparisons by biological sex or self-identified gender including transgender)
5. **R**eligion (e.g. comparisons made by religious affiliation – including non-religious – or religious commitment)
6. **E**ducation (e.g. comparisons by level of education attained)
7. **S**ocioeconomic status (while there may be overlap with education, tends to be income-related such as household income, type of dwelling etc.)
8. **S**ocial capital (refers to social relationships or networks, or community or civic partnerships. Examples include comparisons between isolated individuals or individuals living alone vs households with multiple members)
9. Other (e.g. disease status or presence of comorbidities or disabilities)
10. No subgroup analyses conducted

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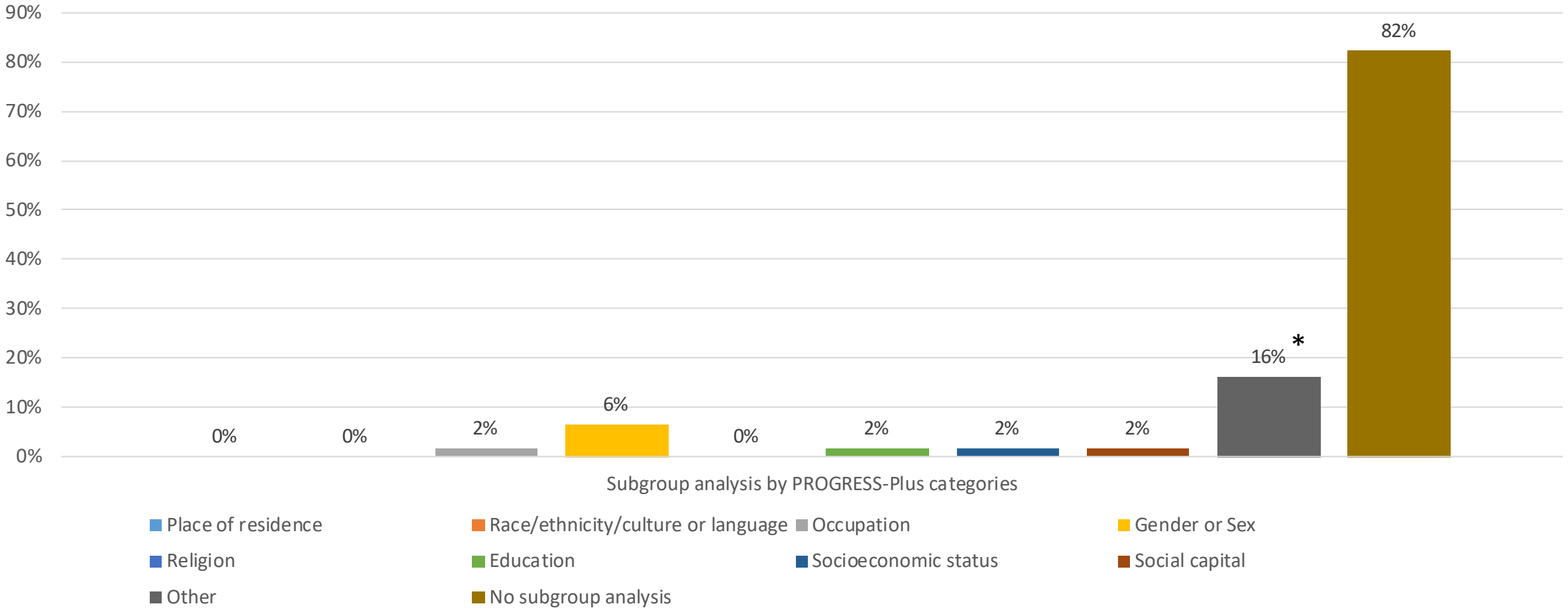
For further elaboration on the PROGRESS framework see: O'Neill, J., H. Tabish, V. Welch, M. Petticrew, K. Pottie, M. Clarke, T. Evans, J. Pardo Pardo, E. Waters, H. White and P. Tugwell (2014). "Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health." Journal of Clinical Epidemiology 57: 56-64.

Subgroup analyses: PROGRESS-Plus (N=62)



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* 9/10 listed as other were based on disease severity

Data extraction

Ethical issue	• Data extraction
Research/care distinction	• Did the manuscript report on ethics review? • If not submitted, why? If deemed exempt, why?
Subject identification/populations affected by the trial – including vulnerable groups and equity considerations	• Who was the research subject (patient with dementia, caregiver, healthcare professional, other)? • Explicit consideration of vulnerable groups and special protections • Explicit consideration of equity or differential effect of treatments
Informed consent, including waivers of consent and role of notification	• Was there any statement about individual level consent? • Was capacity to consent explicitly stated either as a requirement within the inclusion criteria or through the explicit exclusion of participants without capacity to consent? • For studies where the requirement for consent was not waived, was an assessment of capacity conducted with patients? (If yes, what tool or assessment measure was used?) • If consent was sought, for which aspects of the trial was consent sought? • What modes were used for obtaining consent (e.g. verbal, written etc)

Individual-level consent

- No explicit mention of waiver of consent in any study
- 55/62 (89%) studies involved patients with dementia and reported individual level consent was obtained
  - Over half (51%) failed to specify what consent was for (e.g. data collection, intervention)
  - 41/55 (75%) studies employed a substitute decision-maker (proxy consent) for at least some patients (e.g. if patient could not provide individual consent)
  - 9/55 (16%) studies reported patient assent
  - 16/55 (29%) studies explicitly reported a capacity assessment relating to individual consent
    - Only 4 studies described the tool or framework used to assess capacity

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Discussion

Take home messages

- Pragmatic RCTs raise a number of ethical issues
  - research/practice distinction, human subject identification (including vulnerability, special protections, and equity), consent, gatekeepers, and implications from non-clinical settings.
- Each potentially pose challenges for ethics review and regulation
- Empirical studies of published pragmatic RCTs are challenging due to complexity of the concept of pragmatism, incomplete reporting, and suboptimal indexing
  - Relying on the use of the term pragmatic or indexing of trial likely to miss a large proportion of likely pragmatic RCTs
- However, our validated search filter showed excellent specificity and yielded over 4000 trials

Take home messages

- Published pragmatic RCTs in ADRD or with PLWD are highly diverse
  - Many with cluster design, but patient level research-specific data collection
- Human subject identification is complex
  - Studies focused on patients, caregivers, and healthcare professionals. A large proportion of cluster RCTs and health policy/system interventions which add further complexity
- Many ADRD studies relied on **substitute decision makers**.
  - Need for improved reporting (and/or practice) regarding when and how decisions about substitute decision makers are made.
  - Few additional special protections noted, despite explicit inclusion of vulnerable populations
- Few studies conducted subgroup analyses

Acknowledgements

- Monica Taljaard
- Kelly Carroll
- Hayden Nix

- CIHR Ethics of Pragmatic trials team
  - ***Monica Taljaard***, Charles Weijer, Jeremy M. Grimshaw, Jamie C. Brehaut, Marion K. Campbell, Kelly Carroll, Sarah Edwards, Sandra Eldridge, Bruno Giraudeau, Cory E. Goldstein, Ian D. Graham, Karla Hemming, ***Spencer Phillips Hey***, Vipul Jairath, Terry P. Klassen, ***Alex John London***, Susan Marlin, John C. Marshall, Lauralyn McIntyre, Joanne E. McKenzie, Stuart G. Nicholls, P. Alison Paprica, Merrick Zwarenstein and Dean A. Fergusson
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