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BRIEF COMMUNICATION

Trials with proxy-reported outcomes registered on the Australian New Zealand Clinical Trials Registry (ANZCTR)

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Abstract

Aims A proxy is someone other than a patient who reports a patient's outcomes as if they are the patient. Due to known discordance with patient reports, proxies are often not recommended in clinical trials; however, proxies may be needed in certain research contexts. We aimed to identify and describe trials registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) with proxy-reported endpoints.

Methods ANZCTR was systematically searched from inception (2005) to 31 March 2017 for trials with proxy-reported endpoints. Primary and secondary endpoints for each trial retrieved by the search were individually coded (proxy-reported: yes/no), and trials with confirmed proxy-reported endpoints were included in the analysis.

Results Of 13,666 registered trials, 469 (3.4%) included a proxy-reported endpoint (867 individual proxy-reported endpoints in total: 62% family member proxy, 22% health professional). Proxy endpoint inclusion did not significantly increase over time ($r=0.18$, $p=0.59$). Mental health (11.5%), stroke (10.3%) and neurological (8.3%) trials had the highest proportion of trials using proxies. Of the 469 trials, 123 (26.2%) studies involved paediatric patients.

Discussion Proxy-reported endpoints are included in a small but notable number of studies, which may indicate other types of outcomes are used for patients unable to self-report, or that these patients are under-researched.

Keywords Proxy-reported outcomes · Quality of life · Clinical trial registration · Clinical trial endpoint · Outcome measures

Introduction

The importance of assessing patient-centred outcomes is widely recognised. Patient-reported outcomes (PROs) assess the patient's perspective of the impact of disease and treatment. PRO assessment inherently requires that the patient is reliably able to self-report their outcomes. However, patient-centred outcomes are equally important for patients who are unable to self-report due to their age, disease, condition or treatment. In such cases, proxy reporters may be engaged to report the patient's outcomes as though they were the patient [1]. Proxy reporters may be used in studies of young children, of people with dementia or cognitive impairment, or in studies of critical care, geriatric care or palliative care populations.

Previous studies have shown that discrepancies often exist between proxy and patient reports, particularly for unobservable outcomes [2, 3]. Hence, regulatory agencies often do not encourage proxy use [1] (although the European Medicines Agency has noted proxies may be used if patients are unable to self-report [4, 5]). In contrast, the European Association for Palliative Care's White Paper acknowledged the need for and recommended proxy options for PROs in palliative care [6]. To understand the use of proxy-reported

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Note that categories marked with* are not mutually exclusive [9].

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outcomes in clinical trials in light of these conflicting stances across countries and health conditions, we aimed to identify and describe key features of clinical trials and observational studies that use proxy-reported outcomes registered with the Australian New Zealand Clinical Trials Registry (ANZCTR).

Methods

ANZCTR

The ANZCTR is an online registry of trials being undertaken in Australia, New Zealand and other countries internationally and is recognised by the World Health Organization International Clinical Trials Registry Platform as a Primary Registry [7].

Search strategy

Our search strategy has been reported previously [8]. Briefly, the "Outcomes" and "Statistical methods/analysis" fields of the ANZCTR were systematically searched from inception (2005) to 31 March 2017. The search comprised of 2650 terms in total, including full titles and acronyms of PRO and proxy measures, and key terms (e.g. "proxy", "quality of life", "health status", "Likert scale", "Visual analog* scale"). Search results and key summary data on each trial (e.g. primary/secondary endpoints, clinical population, recruitment countries, funding source) were exported into Microsoft Excel by a representative from ANZCTR.

All reviewers completed a pilot-coding exercise (~200 trial endpoints each), to determine whether or not each endpoint was proxy-reported. Pilot codes were checked (RMB or DW) for consistency and accuracy before remaining trials were divided among team members for coding.

Proxy endpoints were next categorised according to who acted as the proxy: family member, health professional, researcher, unclear. Trials with at least one proxy-reported endpoint were included in the analysis. The final spreadsheet was checked in full to ensure that all trials coded as having a proxy-reported endpoint were included in the analysis. Findings were summarised according to ANZCTR categories [9] using descriptive statistics.

To estimate the number of paediatric studies (infants, children and adolescents) using proxies, we searched the "health condition" field for all trials with a proxy-reported endpoint for the following key words: "child*", "adolescen*", "infan*", "baby", "birth", "school age", "young", "youth", "p$ediatric*", "neonatal", "*school*", "toddler", "parent", "mother" "father", "maternal" and "paternal". The "health condition" field is a free text field to describe study populations within ANZCTR and up to 20 conditions can be added per trial [9].

We computed a Pearson correlation coefficient to test for a linear relationship between year of trial registration (trials registered 2006–2016; the years for which ANZCTR data were available for the full calendar year) and rate (%) of registered trials with any proxy-reported endpoints for each year. All analyses were performed in Microsoft Excel, R-Studio (v1.0.136) and SPSS, V24.0. Armonk, NY:IBM.

Results

On 31 March 2017, the ANZCTR database included 13,666 registered trials [10]. Our search identified 8512 trials (51,443 trial endpoints) for screening, and 469 trials (3.4%) included at least one proxy-reported endpoint (867 individual proxy-reported endpoints across the 469 trials. 195 trials had two or more proxy endpoints). Only 3.6% of interventional trials and 2.1% of observational studies registered on ANZCTR included proxy-reported endpoints (Table 1). 291 trials included both a PRO and a proxy-reported endpoint.

The five condition categories* in which proxy-reported endpoints were most prevalent, as a percentage of trials within that category, included mental health (11.5%), stroke (10.3%), neurological (8.3%), human genetics and inherited disorders (7.4%) and ear conditions (6.6%).

Behaviour interventions (8.3%) and "other" treatment modes (4.6%; see [9] for description) were the most common types of interventions* among studies that used proxy measures.

Studies funded by charities, societies or foundations (23.7%) and government bodies (23.3%) had the highest proportions of studies with proxy-reported outcomes.

Studies recruiting from* Australia and North America each included proxy-reported endpoints in 4.0% of studies. New Zealand included proxies in 3.0% and UK/Ireland in 2.9% of studies.

Based on our hand-search of "health condition", a minimum of 123 paediatric studies included proxies, which is 26.2% of all proxy studies identified in this research (Table 2).

Figure 1 shows the number of trials registered on ANZCTR over time with proxy-reported endpoints, and overall. There was no evidence of a relationship between date of registration and the inclusion of proxy-reported endpoints ($r = 0.18$, $p = 0.59$).

Table 3 shows the relationship between the patient and the proxy. Of the 867 proxy-reported endpoints (across 469 trials), family members and health professionals acted as proxies for 62% and 22%, respectively.

Table 1 Characteristics of 469 studies with proxy-reported endpoints

	Overall ANZCTR until 31 March 2017 ($N=13,666$)		Trials with proxy-reported endpoints ($n=469$)		% with proxy-reported endpoints of that category[c]
	N ANZCTR	% ANZCTR[a]	N with proxy-reported endpoints	% of trials with proxy-reported endpoints[b]	
Type					
Interventional	12,099	88.5	436	93.0	3.6
Observational	1567	11.5	33	7.0	2.1
Condition category[d]					
Mental health[f]	1840	13.5	211	45.0	11.5
Stroke	301	2.2	31	6.6	10.3
Neurological[g]	956	7	79	16.8	8.3
Human genetics and inherited disorders	162	1.2	12	2.6	7.4
Ear	76	0.6	5	1.1	6.6
Public health	1273	9.3	75	16.0	5.9
Injuries and accidents	453	3.3	24	5.1	5.3
Physical medicine/rehabilitation	1053	7.7	44	9.4	4.2
Respiratory	1011	7.4	32	6.8	3.2
Diet and nutrition	1119	8.2	35	7.5	3.1
Cancer	1511	11.1	44	9.4	2.9
Skin	288	2.1	8	1.7	2.8
Alternative and complementary medicine	408	3	11	2.3	2.7
Oral and gastrointestinal	694	5.1	16	3.4	2.3
Anaesthesiology	956	7	21	4.5	2.2
Inflammatory and immune system	458	3.4	10	2.1	2.2
Surgery	734	5.4	15	3.2	2.0
Infection	690	5	14	3.0	2.0
Other	408	3	8	1.7	2.0
Musculoskeletal	1256	9.2	18	3.8	1.4
Reproductive health and childbirth	863	6.3	12	2.6	1.4
Cardiovascular	1295	9.5	13	2.8	1.0
Metabolic and endocrine	1047	7.7	9	1.9	0.9
Renal and urogenital	474	3.5	4	0.9	0.8
Eye	312	2.3	1	0.2	0.3
Blood	258	1.9	0	0.0	0.0
Intervention[d]					
Behaviour	1593	11.7	132	28.1	8.3
Treatment: other[e]	3261	23.9	151	32.2	4.6
Rehabilitation	1122	8.2	43	9.2	3.8
Prevention	1941	14.2	71	15.1	3.7
Other intervention	684	5	24	5.1	3.5
Lifestyle	1216	8.9	39	8.3	3.2
Treatment: devices	1495	10.9	43	9.2	2.9
Treatment: drugs	3490	25.5	94	20.0	2.7
None/N/A	1281	9.4	31	6.6	2.4
Treatment: surgery	526	3.8	12	2.6	2.3
Early detection/screening	443	3.2	9	1.9	2.0
Diagnosis/prognosis	452	3.3	5	1.1	1.1
Primary funding source					
Charities/societies/foundations	545	4	129	27.5	23.7
Government body	738	5.4	172	36.7	23.3

Table 1 (continued)

	Overall ANZCTR until 31 March 2017 ($N=13,666$)		Trials with proxy-reported endpoints ($n=469$)		% with proxy-reported endpoints of that category[c]
	N ANZCTR	% ANZCTR[a]	N with proxy-reported endpoints	% of trials with proxy-reported endpoints[b]	
Collaborative group	418	3.1	18	3.8	4.3
Other	442	3.2	17	3.6	3.8
Commercial sector/industry	1478	10.8	52	11.1	3.5
Hospital	2359	17.3	58	12.4	2.5
University	4082	29.9	92	19.6	2.3
Self-funded/unfunded	3591	26.3	37	7.9	1.0
Not specified	738	5.4	0	0.0	0.0
Recruitment countries[d]					
Australia	9672	70.8	389	82.9	4.0
North America	376	2.8	15	3.2	4.0
New Zealand	2057	15.1	62	13.2	3.0
UK and Ireland	244	1.8	7	1.5	2.9
Europe	1438	10.5	30	6.4	2.1
Africa	341	2.5	7	1.5	2.1
Middle East	443	3.2	9	1.9	2.0
Asia	887	6.5	18	3.8	2.0
South America	401	2.9	3	0.6	0.7
Oceania	23	0.2	0	0.0	0

[a]Calculated as: *n* trials within the category (all trial endpoints)/all 13,666 trials in ANZCTR

[b]Calculated as: *n* trials with Proxy-reported endpoints within the category/all 469 trials with Proxy-reported endpoints

[c]Calculated as: *n* trials with Proxy-reported endpoints within the category/n trials within the category (all trial endpoints)

[d]Studies could select up to three categories as appropriate

[e]May include "exercise, physiotherapy, cognitive therapy, special diets, herbal medicines, web-based treatments, motivational classes, music therapy, stem cell interventions" [9]

[f]Including individuals with learning disabilities and Autistic spectrum disorders [9]

[g]Dementia, Parkinson's disease, Alzheimer's, Transmissible spongiform encephalopathies, epilepsy, Multiple Sclerosis, neurodegenerative diseases and other studies of the disordered or normal brain and nervous system [9]

Discussion

This study is, to our knowledge, the first to estimate the use of proxies in health research. Few ANZCTR trials overall (3.4%) included proxy-reported endpoints. However, there were some contexts in which proxy reporters were used in a notable portion of studies, including mental health, stroke and neurological conditions. Many of these conditions manifest with problems with communication or cognitive processing; therefore, proxy use in these contexts is unsurprising. Not all clinical trials are amenable to proxy assessment; therefore, the low rates of use must be interpreted carefully.

Past studies involving paired data from patients and proxies have documented a phenomenon known as "cross informant variance", whereby proxies reported poorer outcomes compared to patients [2, 11]. Precise levels of discordance are unknown outside of paired studies, and thus is difficult to adjust for statistically [12]. This may be a barrier to the implementation of proxy-reported endpoints for some researchers.

Family members most frequently fulfilled the proxy role. Family members are well placed as proxies because they often act as primary caregivers and spend considerable time with the patient. Limited research exists comparing the accuracy of family caregivers and health professionals as proxies. One study of terminally ill cancer patients found that family caregivers were more accurate, and improved as the patients' disease progressed; however, the range of agreement between patient-family member proxy dyads ranged considerably [13]. Steel and colleagues compared clinician and family proxy reports for hepatocellular carcinoma patients and found that family proxy reports were more consistent with patient reports for physical and functional well-being and additional concerns [14]. This previous research demonstrating higher accuracy of family member proxies as compared to non-family member proxies may explain the

Table 2 Condition categories of 123 paediatric studies with proxy-reported endpoints

Condition category[a]	*n* studies	% of all 469 ANZCTR studies with proxy endpoints
Mental health[b]	92	19.6
Public health	30	6.4
Diet and nutrition	15	3.2
Neurological[c]	10	2.1
Cancer	5	1.1
Anaesthesiology	5	1.1
Oral and gastrointestinal	4	0.9
Respiratory	3	0.6
Physical medicine/rehabilitation	2	0.4
Surgery	2	0.4
Other	2	0.4
Reproductive health and childbirth	2	0.4
Human genetics and inherited disorders	1	0.2
Ear	1	0.2
Injuries and accidents	1	0.2
Infection	1	0.2
Musculoskeletal	1	0.2
Total unique paediatric proxy studies	123	26.2

[a]Studies could select up to three categories as appropriate

[b]Including individuals with learning disabilities and Autistic spectrum disorders [9]

[c]Dementia, Parkinson's disease, Alzheimer's, Transmissible spongiform encephalopathies, epilepsy, Multiple Sclerosis, neurodegenerative diseases and other studies of the disordered or normal brain and nervous system [9]

higher proportion of family caregiver proxies used in practice in ANZCTR.

Studies of infants, children and adolescents comprised over a quarter of all ANZCTR proxy studies. This should be considered a minimum estimate because the "health condition" field of the ANZCTR (the basis of our search for such studies) is entered by trial investigators via free text [9] and terminology used by investigators may have differed to what we included in our search. Higher use of proxy reporters in paediatric studies was anticipated. Often, a child can self-report upon reaching a certain age, whereas in other contexts, the time of conversion to self-report may depend on the developmental abilities of the child [15]. Many of the most commonly used paediatric PRO measures have both child- and parent-reported versions [16–18]. Of note, the Patient-Reported Outcome Measurement Information System (PROMIS) has a comprehensive, carefully developed and validated suite of parent proxy measures [17, 19]. The availability of well-developed proxy measures may arguably be linked with their higher rate of use in paediatric populations.

Unlike PRO endpoints, which increased in frequency over time in ANZCTR [8], there was no relationship between the percentage of trials that included proxy-reported outcomes and time. This may reflect (1) the position of regulatory bodies such as the Food and Drug Authority (FDA, USA) which discourages proxy assessment, (2) that certain clinical groups are under-researched with respect to patient-centred outcomes or (3) increased use and preference for aptitude-based or observer-reported endpoints among these research populations. It may also reflect a lack of guidance for, and hence, confidence in the use of proxy-reported endpoints. Guidance may help ensure proxy studies are conducted to a high standard, as studies continue to use proxy reports despite the challenges associated with their implementation, analysis and interpretation.

The strengths of this study include a comprehensive search and screening strategy of a large, international trial registry belonging to the WHO network [7]. A possible limitation is unclear generalisability—our results may not reflect the extent to which proxy-reported endpoints are used in studies internationally. There is potential we have missed ad hoc proxy measures not captured by our search. It was not possible to calculate the proportion of all paediatric studies including proxies. More international research on the use of proxies in health research is needed.

In conclusion, proxy-reported endpoints are used in a small portion of ANZCTR studies, most commonly in studies of young people, mental health, stroke and neurological conditions. Our data may be used to identify

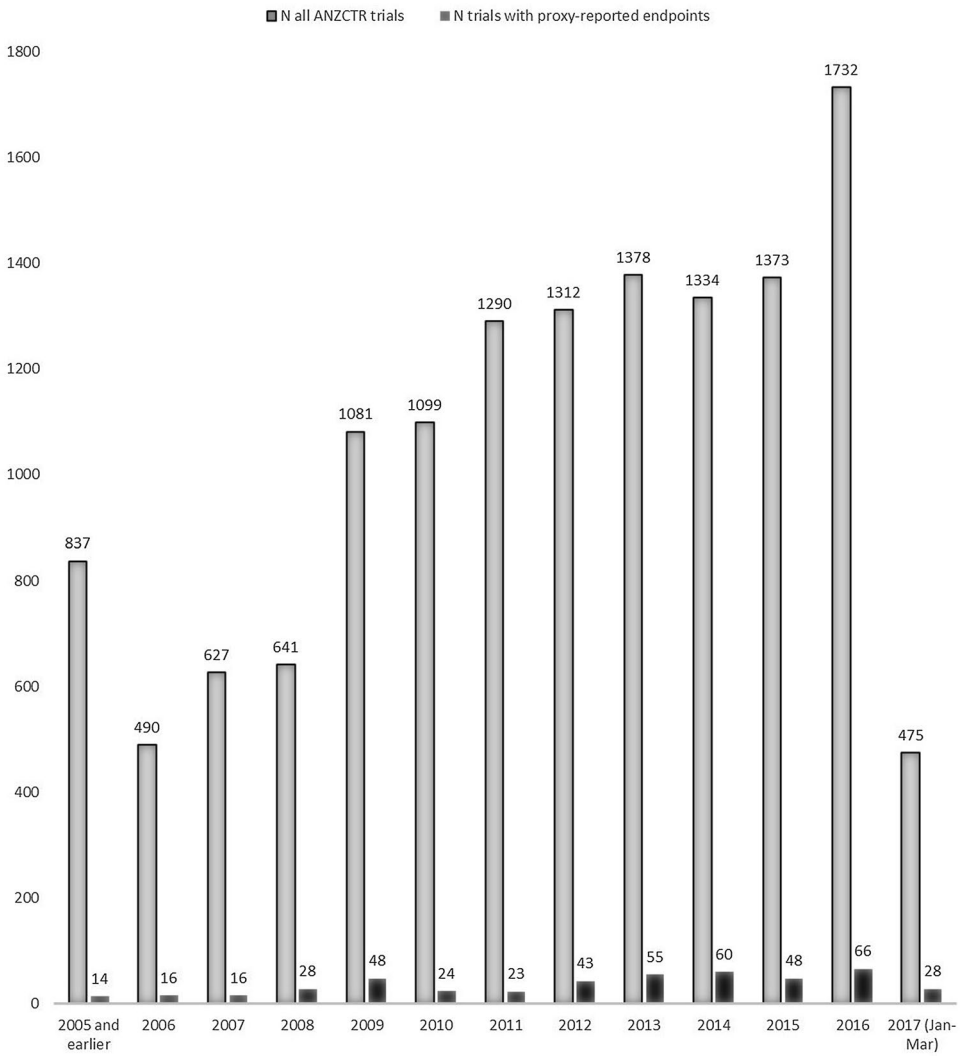

Fig. 1 Trials registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) each year: all registered versus trials with proxy endpoints

Table 3 Relationship of proxy reporter to the patient, $n = 867$ proxy endpoints across 469 trials

Proxy-reporter type	*n*	%
Family member/primary caregiver (e.g. spouse, parent, child)	536	62
Health professional (e.g. nurse, clinician)	191	22
Unclear/unspecified proxy reporter	126	15
Researcher	7	0.8
Both family member and health professional	7	0.8

research contexts with high use of proxies, to target future methodological work and generate hypotheses about the use of proxy measures. It also sheds light on current methodologies for studying patients who are unable to communicate independently.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval The University of Sydney Human Research Ethics Committee does not review studies that do not include human participants and therefore human research ethics approval was not required for this study.

Informed consent We obtained permission from the ANZCTR to conduct this research. No human research participants were involved in this study, therefore informed consent was not required.

Research involving human and animal participants In accordance with the University of Sydney's (sponsor) ethical procedures, this research

did not include human research participants and therefore human research ethics approval was not required. The data included in this study are publically available on ANZCTR and concerns clinical trial information. No human data were included in this analysis.

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