AGE AND AGEING

TITLE PAGE

TITLE: The uptake of the hip fracture core outcome set: analysis of 20 years of hip fracture trials

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ABSTRACT

BACKGROUND: Clinical trials test the effectiveness or efficacy of treatments. It is important that researchers evaluate interventions with the most meaningful outcome measures. The 2014 hip fracture core outcome set recommended that mortality, mobility, pain, activities of daily living and health related-quality of life (HRQOL) should be assessed in all trials of patient with hip fracture. The purpose of this analysis was to determine the uptake of these recommendation.

METHODS: All trials registered from 1997 to 2018 recruiting participants following hip fracture were identified from the ClinicalTrials.gov trials registry. The frequency of each core domain adopted annually were assessed.

RESULTS: 311 trials were identified and analysed. On analysing trial registries for years which presented a minimum of 10 registrations, full core outcome set adoption ranged from 0% (2017; 2018) to 24% (2009). Mortality and mobility were the most consistently reported domains (mortality: 27% (2017) to 56% (2011); mobility: 36% (2015) to 60% (2004)). In contrast, pain and HRQOL were least reported (pain: 14% (2017) to 61% (2015); HRQOL: 10% (2010) to 11% (2008)). There was no clear change in core outcome domain set adoption following the publication of Hayward et al's (2014) core outcome set.

CONCLUSIONS: There has been limited adoption of the hip fracture core outcome set from its publication in 2014. Further consideration to improve implementation is required to improved uptake.

Keywords: Hip fracture; trials; research; outcomes

Key points:

- Researchers should base their choice of outcome measures on core outcome set recommendations.
- The current hip fracture core outcome set has limited uptake across all five recommended domains since its 2014 publication.
- Further investigation is required to determine why researchers are not using this core outcome set when designing hip fracture trials.

INTRODUCTION

Clinical trials determine whether an intervention is effective for patients by comparing their effects on outcome measures chosen to identify benefit or harm relative to usual care or a different intervention [1]. The reported effects on outcome measures are used to make decisions on whether treatments are recommended for clinical practice. It is therefore essential that outcome measures reported in trials are important for patients, clinicians and wider decision-makers.

A core outcome set is an agreed recommended list of domains which researchers should assess, and includes a consensus on measures to be used [2]. It consists of 'domains' and 'instruments'. A domain is a specific 'area' which should be measured i.e. quality of life, healthcare costs, body function, biomarkers. An instrument is the outcome measure which measures that specific domain i.e. questionnaires to assess quality of life, scales to assess cost, measures of body function, and tests and imaging to assess biomarkers. By following a core outcome set, researchers are better informed in their selection of outcome measures. There is also reduced risk of inconsistent reporting in outcome measures which can be a barrier to evidence synthesis [4].

Core outcome sets are most frequently developed through a process including: (1) literature reviews to identified relevant domains; (2) qualitative research to gain views from patients, clinicians and other stakeholders on important domains; and (3) agreement on domain selection through Delphi exercises and consensus meetings [3]. Once domains have been identified, instruments to measure these domains are determined through literature reviews, before the potential instruments are analysed for their clinimetric properties to establish the best instruments available to measure each domain [3].

Hayward et al [5] were the first to report a core outcome set for all hip fracture trials. They identified five domains following a series of consensus meetings across stakeholder groups. These were mortality, pain, activities of daily living, mobility, and health-related quality of life (HRQOL) [5]. It is not known whether the publication of this core outcome set led to changes in selection of outcome measures in hip fracture trials. Therefore, this study aims to: 1) analyse the temporal trends in outcome measure selection in hip fracture trials; and 2) determine whether outcome measure selection changed with the publication of the core outcome set for hip fracture trials.

METHODS

We adopted Kirkham et al's [6] approach to core outcome set assessment using a trial registration database. This is an efficient means of estimating uptake compared to published trial reports [6,7]. We searched the trial registry ClinicalTrials.gov to identify all trials registered from 1st January 1997 to 1st May 2018, recruiting people with hip fracture. The following filters were applied to identify eligible trials: "conditions: hip fracture". No restriction was placed on the type of study or the phase of trial.

From all eligible trial registrations, data were extracted for each component of the core outcome set for hip fracture trials [5]. These were: mortality; pain; activity of daily living; mobility and HRQOL. If a trial had registered a composite outcome, we considered all individual outcomes in the composite. Data extraction also included: year of registration, country of origin, sample size, age of participants recruited; funding source (industry vs. research council vs. mixed), study design (randomised controlled trial (RCT) vs. non-RCT), duration of follow-up, whether participants with cognitive impairment were eligible for trial enrolment, the intervention type under investigation (drug or non-drug trial/surgical or non-surgical) and phase of trial.

All trial registry entries were reviewed and extracted by one reviewer (TS). An independent reviewer (TC) reviewed a random sample of 30% (n=93) of the data collected to ensure data extraction accuracy. Disagreements in data extracted were resolved through discussion. Where available, full-text protocols, trial publications, or study reports were reviewed to verify data (n=83). These were identified through the MEDLINE and EMBASE databases via the Ovid Platform. When data differed (n=6), the data from the final report was included in the data extraction table. For trial registry entries where a publication could not be identified (n=228), the corresponding researcher named on the trial registry was emailed and asked to verify the core outcome set data.

Data Analysis

We reported the frequency of registered hip fracture trials which reported each component of the core outcome set. These were assessed from 1997 to 2018. We also assessed whether the frequency of core outcome set adoption changed after the publication of the 2014 Hip Fracture core outcome set [5]. Analyses were made assessing each year where a minimum of 10 trials were registered.

RESULTS

Characteristics of trial registrations

In total, 311 trial registries were identified (**Supplementary Figure 1**). The characteristics of these are presented in **Supplementary Table 1** and **Supplementary Table 2**. In total, 43% of trials were registered in Europe, 24% in Asia and 31% in North America. Trials had a mean sample size of 196 participants (Standard Deviation (SD): 299) and mean trial duration of 9.4 months (SD: 17.2). Fifty-five percent of trials excluded participants with cognitive impairment.

Uptake of core outcome set

Table 1 illustrates the distribution of core outcome set adoption from 1997 to 2018. Full core outcome set adoption ranged annually from 0% (Years 1997-1999,2001,2003,2005,2006,2007,2018) to 100% (Year 2000). On analysing trial registries for years which presented a minimum of 10 registrations, full core outcome set adoption ranged from 0% (2017; 2018) to 24% (2009) (**Figure 1**). Mortality and mobility were consistently the most reported domains. Mortality ranged from 27% (2017) to 56% (2011), whilst mobility ranged from 36% (2015) to 60% (2004). In contrast, pain and HRQOL were the least reported domains. Pain was reported in 14% (2017) to 61% (2015) of trial registries per year, whilst HRQOL was reported in 10% (2010) to 11% (2008) per year. There was no clear change in core outcome set domain adoption following the publication of Hayward et al's [5] core outcome set.

DISCUSSION

This analysis indicates infrequent use of the full core outcome set for hip fracture trials. None of the five domains are consistently reported before or after the core outcome sets publication [5]

It is not clear whether the hip fracture core outcome set is not considered fit for purpose during trial development, or whether it is fit for purpose but not being adopted. For the former, the limited stakeholder involvement in the development of the hip fracture core outcome set may undermine its fitness for purpose [5]. Indeed, Tunis et al [10] and organisations developing core outcome sets (e.g. COMET and OMERACT) recommend a strategy to improve stakeholder engagement (patients, clinicians, industry and regulatory authorities) during development. For the latter, promotion of the core outcome set may be required. Through wider awareness of its existence, the applicability of the core outcome set to a breath of trials may be explored. For example, the core outcome set may be more applicable to surgical compared to anaesthetic or rehabilitation trials. Further consultation with increased engagement of the wider research community may therefore be an important step to address the reported limited uptake.

Mortality was the most frequently consistent domain reported. This however remained low, ranging from 27% (2017) to 56% (2011) when 10 or more registries were published in a given year. Given that trials should report adverse events in accordance with Good Clinical Practice [11], the collection of this data should be mandatory. This may be attributed to either trials not collecting this data or researchers considering this a regulatory requirement and not a specific outcome measure. Clear reporting of trial protocols and methodologies is a cornerstone to the SPIRIT [12] and CONSORT [13] recommendations. Promotion of the core outcome set with clear reporting of the outcome measures is paramount.

Haywood et al [5] did not recommend instruments for measuring the domains identified in the core outcome set. Such guidance should only be made once the validity and reliability of outcome measures for a specific domain have been evaluated. When used in combination with agreed trials end points, as being developed in perioperative trials through the Standardized Endpoints in Perioperative Medicine (StEP) initiative, researchers will have clearer guidance on what measures to use and when. This will improve outcomes reporting consistency across trials enabling meta-analyses and clinical guideline formation [14].

We limited our search to ClinicalTrials.gov which may have led to the exclusion of trials indexed in other registries. Further, we did determine the proportion of published trials which adopted the core outcome set. We believe trials identified in this paper are likely to be a representative sample as all registries endorsed by the International Committee of Medical Journal Editors must meet common standards, and most journals require trial registration for publication.

CONCLUSIONS

The choice of which outcome measures to use in trials of interventions for hip fracture has not changed following the publication of the 2014 core outcome set. There is limited uptake of the core outcome set. There is a need to determine why uptake is poor. Further consideration of dissemination and wider stakeholder involvement may be warranted.

DECLARATIONS

Ethical Approval: None required for this study design.

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FIGURE AND TABLE LEGENDS

Figure 1: Graph of uptake of core domain for the hip fracture core outcome set from 2004 to 2018 (where 10 or more registrations were recorded per year).

Table 1: Frequency (%) of domains reported and complete adoption of the core outcome set in included trial registrations by year.

Supplementary Table 1: Characteristics of included trials registered on ClinicalTrials.gov

Supplementary Table 2: Country of origin for registered trial protocols

Supplementary Figure 1: Flow-chart of identification of trial registrations from ClinicalTrial.gov database

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Figure 1: Graph of uptake of core domain for the hip fracture core outcome set from 2004 to 2018 (where 10 or more registrations were recorded per year).

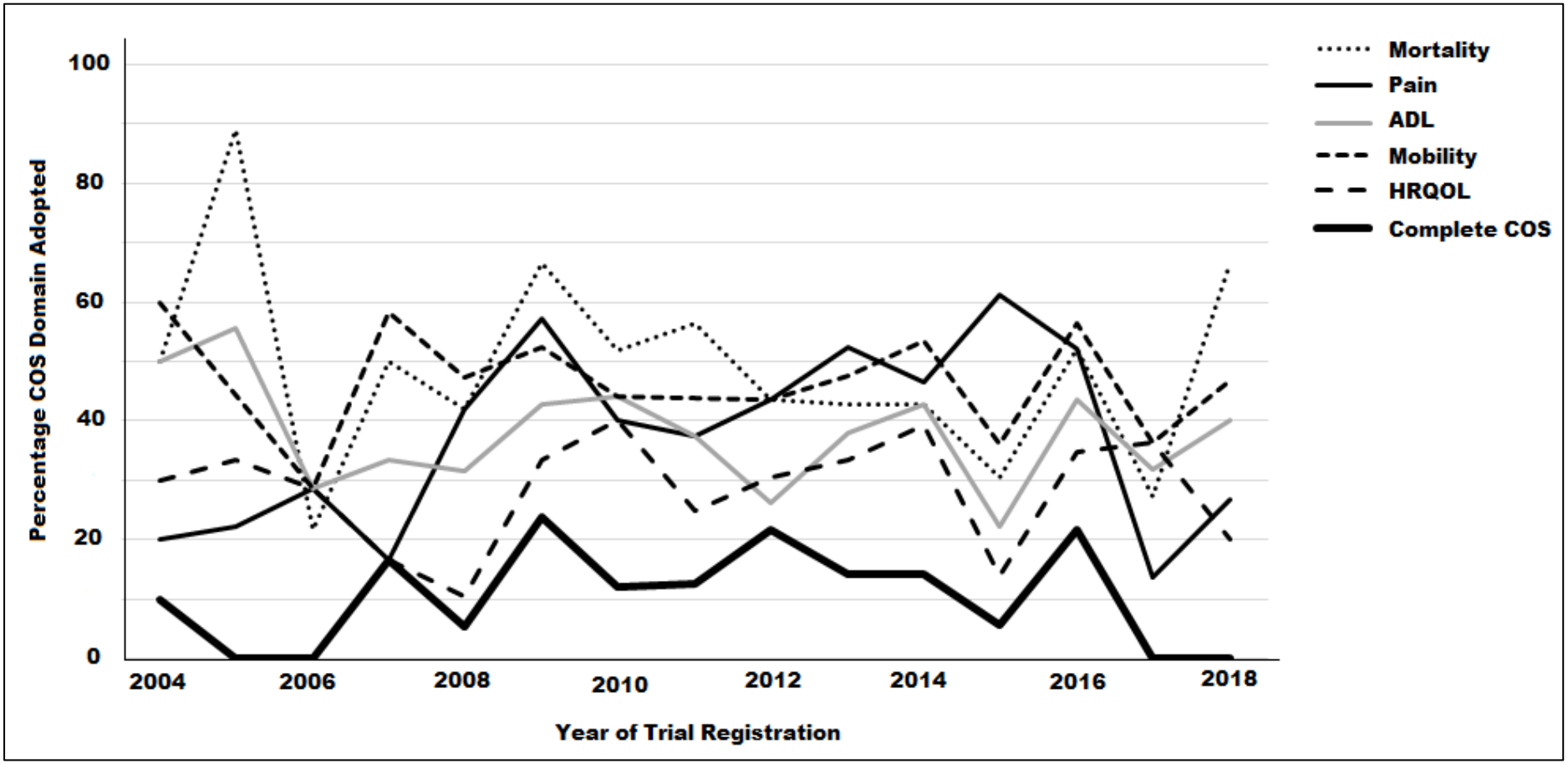

Table 1: Frequency (%) of domains reported and complete adoption of the core outcome set in included trial registrations by year.

Domain	Total	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
N	311	0	1	1	1	1	7	4	10	9	7	12
Mortality	146 (46.9)	0 (0.0)	1 (100)	0 (0.0)	1 (100)	1 (100)	4 (57.1)	2 (50.0)	5 (50.0)	8 (88.9)	2 (28.6)	6 (50.0)
Pain	127 (40.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	3 (42.9)	1 (25.0)	2 (20.0)	2 (22.2)	2 (28.6)	2 (16.7)
ADL	116 (37.3)	0 (0.0)	1 (100)	1 (100)	1 (100)	1 (100)	2 (28.6)	1 (25.0)	5 (50.0)	5 (55.6)	2 (28.6)	4 (33.3)
Mobility	143 (46.0)	0 (0.0)	1 (100)	1 (100)	1 (100)	0 (0.0)	3 (42.9)	1 (25.0)	6 (60.0)	4 (44.4)	2 (28.6)	7 (58.3)
HRQOL	91 (29.3)	0 (0.0)	1 (100)	1 (100)	1 (100)	1 (100)	3 (42.9)	0 (0.0)	3 (30.0)	3 (33.3)	2 (28.6)	2 (16.7)
All COS	37 (11.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	2 (28.6)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (16.7)
		2008	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
N		19	21	25	16	23	21	28	36	23	22	15
Mortality		8 (42.1)	14 (66.7)	13 (52.0)	9 (56.3)	10 (43.5)	9 (42.9)	12 (42.9)	11 (30.6)	12 (52.2)	6 (27.3)	10 (66.7)
Pain		8 (42.1)	12 (57.1)	10 (40.0)	6 (37.5)	10 (43.5)	11 (52.4)	13 (46.4)	22 (61.1)	12 (52.2)	3 (13.6)	4 (26.7)
ADL		6 (31.6)	9 (42.9)	11 (44.0)	6 (37.5)	6 (26.1)	8 (38.1)	12 (42.9)	8 (22.2)	10 (43.5)	7 (31.8)	6 (40.0)
Mobility		9 (47.4)	11 (52.4)	11 (44.0)	7 (43.8)	10 (43.5)	10 (47.6)	15 (53.6)	13 (36.1)	13 (56.5)	8 (36.4)	7 (46.7)
HRQOL		2 (10.5)	7 (33.3)	10 (40.0)	4 (25.0)	7 (30.4)	7 (33.3)	11 (39.3)	5 (13.9)	8 (34.8)	8 (36.4)	3 (20.0)
All COS		1 (5.3)	5 (23.8)	3 (12.0)	2 (12.5)	5 (21.7)	3 (14.3)	4 (14.3)	2 (5.6)	5 (21.7)	0 (0.0)	0 (0.0)

ADL – activities of daily living; COS – core outcome set; HRQOL – health-related quality of life; N – number of trial registrations

Supplementary Table 1: Characteristics of included trials registered on ClinicalTrials.gov

Characteristic	Number (%) of trials (N=311)
Trial Phase	
1	7 (2)
2	22 (7)
3	42 (14)
4	61 (20)
5	23 (7)
Not stated	156 (50)
Study Type	
Interventional	309 (99)
Reliability of Assessment Methods	1 (0.3)
Diagnostic Test Accuracy of Imaging Modality	1 (0.3)
Trial Design	
RCT	269 (87)
Non-RCT	42 (14)
Intervention Type	
Surgical	99 (32)
Perioperative General	84 (27)
Pre-operative	20 (6)
Intra-operative (non-surgical)	68 (22)
Rehabilitation	40 (13)
Trial duration	
Mean duration (months; SD)	9.38 (17)
Not documented	11
Planned sample size	
Mean sample size (SD)	195.5 (299)
Not documented	3 (1)
Trial status	
Complete	133 (43)
Recruiting	62 (20)
Terminated	23 (7)
Not yet recruiting	12 (4)
Active, not recruiting	18 (6)
Withdrawn	10 (3)
Suspended	1 (0)
Enrolling by invitation	1 (1)
Unknown status	51 (16)
Participants with Cognitive Impairment recruited	
Yes	138 (44)
No	170 (55)
Not stated	3 (1)
Funding Source	
Research Council	18 (6)
Industry	48 (15)
Mixed (Research Council & Industry)	0 (0)
Not stated	245 (79)

Principal continent of registration	
Europe	133 (43)
Asia	75 (24)
North America	95 (31)
South America	3 (1)
Australasia	5 (2)
Africa	0 (0)
Antarctica	0 (0)
Year of Registration	
1997-2001	7 (2)
2002-2006	37 (12)
2007-2011	93 (30)
2012-2016	131 (42)
2017-2018	37 (12)
Not documented	6 (2)

RCT – randomised controlled trial; SD – standard deviation

Supplementary Table 2: Country of origin for registered trial protocols

Country of Origin	Frequency (%)
USA	82 (26.4)
China	25 (8.0)
Denmark	23 (7.4)
Israel	23 (7.4)
UK	20 (6.4)
Norway	19 (6.1)
France	18 (5.8)
Spain	14 (4.5)
Sweden	14 (4.5)
Canada	13 (4.2)
Switzerland	9 (2.9)
Netherlands	5 (1.6)
South Korea	5 (1.6)
Taiwan	5 (1.6)
Thailand	5 (1.6)
Australia	4 (1.3)
Turkey	4 (1.3)
Greece	3 (1.0)
Japan	3 (1.0)
Ireland	2 (0.6)
Finland	2 (0.6)
Italy	2 (0.6)
Brazil	2 (0.6)
Tunisia	2 (0.6)
Chile	1 (0.3)
Egypt	1 (0.3)
Germany	1 (0.3)
New Zealand	1 (0.3)
Portugal	1 (0.3)
Singapore	1 (0.3)
Syria	1 (0.3)

Supplementary Figure 1: Flow-chart of identification of trial registrations from ClinicalTrial.gov database