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Patient Reported Outcomes in Atrial Fibrillation Research: Results of a clinicaltrials.gov Analysis

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Abstract

Objectives: We aimed to study how frequently patient reported outcomes (PROs) are collected in registered clinical studies of atrial fibrillation (AF).

Background: Improving symptom burden and quality of life are important goals in the treatment of AF, and are best measured with PROs.

Methods: We analyzed data from clinicaltrials.gov to identify PROs in AF studies. All studies reporting AF as the disease condition were included, and PROs were identified by search terms within the Outcomes Measures. Generic and AF-specific PROs were identified, and assessed by study type and year. Clinicaltrials.gov reporting was compared with published reports of linked studies in PubMed.

Results: From 1999-2018, 1709 studies including AF patients were posted; 238 (14%) included PROs. Collection of PROs was reported in 22% (n=83/386) of trials studying procedural interventions and 11% (n=18/168) of all Phase 3 studies. Among the 238 studies with PROs, most described 'quality of life' (n=194, 82%), and most (n=198, 83%) included only generic (not AF-specific) PROs. Only 17% (n=40) of studies reporting PROs specified a previously-published, AF-specific tool, most commonly the AFEQT (n=20, 8.4%). Among the available PubMed citations of 391 studies, 74 (19%) described collecting a specific PRO tool (n=29 [7.4%] for an AF-specific PRO).

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Conclusions: Despite increased emphasis on the importance of PROs in AF, a minority of registered clinical trials reported collecting PROs, with very few using validated, AF-specific PROs. Improving outcomes that are most important to patients will necessitate increased emphasis on these PROs in pivotal clinical studies.

Condensed Abstract

Improving symptom burden and quality of life are important goals in the treatment of AF, best measured with patient reported outcomes (PROs). We assessed PRO use in AF studies registered in clinicaltrials.gov. From 1999-2018, 1709 studies including AF patients were posted; 238 (14%) included PROs. Only 17% (n=40) of studies reporting PROs specified an AF-specific tool, most commonly the AFEQT (n=20, 8.4%). Among PubMed citations (n=391 studies), 29 (7.4%) described collection of an AF-specific PRO. Despite increased emphasis on PROs in AF, a minority of registered clinical trials reported collecting PROs, with very few using validated, AF-specific PROs.

Keywords

atrial fibrillation; patient reported outcomes; clinicaltrials.gov; quality of life; outcomes

Patient reported outcomes (PROs) have been defined as, "*any report of the status of a patient's health condition that comes directly from the patient (i.e., without interpretation of the patient's response by a clinician or anyone else)*".(1) Understanding patients' perspectives is important for atrial fibrillation (AF) because: (1) the subjective experience can vary dramatically between patients (some are asymptomatic whereas others can have debilitating symptoms); (2) AF occurs more commonly in older patients who often prioritize quality of life over longevity; and (3) substantial resources are frequently devoted to improving patients' health status.(2,3) The burden of AF symptoms can be comparable to that of ischemic heart disease or congestive heart failure,(4) and strategies such as catheter ablation have been shown to improve arrhythmia-free survival and improve health-related quality of life(hrQoL).(5–7) Yet there is limited evidence that aggressive rhythm control (compared to symptomatic treatment with rate control) improves clinical endpoints of stroke and/or mortality, and thus the primary indication for pursuing a rhythm control strategy remains improvement of AF symptoms.(8,9) Despite this, it is unclear whether pivotal studies of AF are directly assessing hrQoL using PROs.(8)

We used data from the clinicaltrials.gov repository to assess the reported use of PROs in clinical studies of patients with AF. The objectives of the current analysis were to (1) measure the proportion of registered clinical studies of AF that included PROs as primary outcome measures; (2) assess trends in use of PROs over time; and (3) assess use of AF-specific PROs versus generic instruments in trials of AF. Results of the clinicaltrials.gov analysis were then validated in PubMed searches for the registered studies.

Methods

We analyzed publicly-available data from the clinicaltrials.gov database to identify registered AF studies that reported use of PROs. Data on all studies registered under the

condition “atrial fibrillation” were downloaded, and up to date as of July 10, 2018. No other search filters were used. The studies were further restricted to only those that indicated “atrial fibrillation” in the Conditions field. Studies were further stratified by inclusion of PRO terms in the reported Outcome Measures (see Supplemental Material). Presence of any PRO term indicated reported use of PROs in the study. These included generic PRO measurement tools, generic terms for PROs (e.g., “quality of life”), as well as named, AF-specific PRO tools.(4,10–12) Clinician reported outcomes (CROs), such as European Heart Rhythm Association or Canadian Cardiovascular Society classifications of AF, were not included. See Supplemental Material for more detailed methods.

Characteristics of studies reporting PRO collection were compared to those that did not report PROs as outcome measures. Reporting of PRO collection was assessed over the duration of the reporting, and stratified by study type (interventional versus observational studies; expanded access was classified as observational) and intervention type (device or procedure only vs. drug only; studies with both types of intervention [or other interventions] were excluded from that stratification). Among studies that did report PROs, the use of generic PRO tools versus AF-specific PROs is described.

PubMed Review

In order to assess under- or over-reporting of PROs in the clinicaltrials.gov database, we searched PubMed for any related citation for each of the identified AF studies. Citations were matched based on clinicaltrials.gov identifier, and full-text manuscripts were reviewed (when accessible). Citations were examined for PRO collection, as part of the study methods, as well as the reporting of PROs results in any citation linked to the respective identifier. Because the objective was to assess study use and collection of PROs, all registered studies were included in the search (both completed and not yet completed), and ‘Rationale and Design’ manuscripts were reviewed for outcomes measures. As the description of possible PROs is variable, citations were examined for (a) any report of measuring quality of life outcomes, (b) the use of a specific tool to collect PROs, and (c) the use of a PRO tool specific to AF. Simply the collection of ‘symptomatic AF’ as an outcome (as interpreted by the clinician) was not considered as a collection of PROs or quality of life.

Statistical Methods

Categorical variables are summarized as number (percentage) and univariate comparisons were performed with Chi-squared. A two-sided p-value of <0.05 was considered significant. All analyses were performed using R (Version 3.5.2) and RStudio (Version 1.1.463),(13) with applicable packages.(14)

Results

We identified 1709 entries in clinicaltrials.gov that included patients with AF and were first posted from October 28, 1999, to June 29th, 2018. Overall, 43% (n=735) were reported as completed (n=260 [35.4%] of completed studies had a linked citation in PubMed; see below), and 90% (n=1534) did *not* have results available on clinicaltrials.gov. Among the 1709 registered AF studies, 238 (14%) reported PROs terms in their Outcome Measures

(Table 1). Those reporting PROs as outcomes versus those not collecting PROs were more likely to be classified as interventional (82% vs. 64%, p<0.001), to be of smaller size (11% targeting >1000 participants, vs. 19%, p<0.001), and more likely to involve a procedural intervention (35% vs. 21%, p<0.001). However, among the 386 studies with specifically a procedural intervention, only 83 (22%) reported collecting PROs.

Proportions of studies reporting PRO collection, by year, are shown in Figure 1 (stratified by study type) and in the Central Illustration (stratified by intervention type). During the period where clinicaltrials.gov data are available, the number of posted studies including patients with AF increased from 382 for the first 10 years of reporting (1999-2009) up to 705 in the most recent 3 years (2015-2018).

Reporting of generic PRO tools and terms, versus AF-specific instruments, are shown in Table 2, stratified by study type. Of the 238 entries that reported PROs, 40 (17%) referenced an AF-specific instrument, and this was not significantly different between interventional or observational studies (p=0.90). Among AF-specific PRO measures, the AFEQT was most commonly cited (n=20, 8.4% of studies with PRO terms). Thirty-five studies reported collecting both an AF-specific and a generic PRO measure, none of which were Phase 3 studies (other either drugs or devices).

PubMed Review

Among the 1709 studies of AF in clinicaltrials.gov, 391 (23%) had at least one citation in PubMed associated with the clinicaltrials.gov registration number (Table 3), including either ‘Rationale and Design’ manuscripts and/or publication of results; the majority of these had >1 full-text article that was available and accessed (n=371, 95% of studies with citations).

Of the 1471 studies without PROs described as outcomes in clinicaltrials.gov, 46 (3%) had PubMed entries that described PRO collection. Among these 46, 36 described a specific PRO tool (e.g., EQ-5D), and 16 described an AF-specific PRO tool. Overall, among all of the 1709 registered studies, 65 (3.8%) describe use of an AF-specific PRO in either the registered outcomes and/or a linked PubMed citation.

Discussion

Over the past few decades, there has been increasing recognition of the importance of PROs in the assessment of important outcomes of clinical research studies, especially in chronic, non-fatal conditions. Our understanding of best methods to create and validate PRO tools has evolved, and new disease-specific measurement tools for AF have been introduced. However, in contrast to our expectations, this analysis of AF studies in the clinicaltrials.gov registry found a low proportion of studies reporting PRO collection and this proportion has not improved over time. Thus, while there has been substantial growth in the number of studies of AF patients, only 1 in 7 include PRO terms as Outcomes Measures. Pivotal phase III and intervention-based studies do not show any substantially higher use of PROs. Lastly, among studies that appeared to report PROs, only 17% included AF-specific PRO tools (versus more generic tools or terms).

While controlling symptoms in patients with AF can be challenging, it is often the most important outcome to patients. Interventions to improve symptoms, particularly those geared towards rhythm control (e.g., catheter ablation) can be costly and are not without risk of harm. Furthermore, while emerging data suggest improved thromboembolic and mortality outcomes in subgroups of AF patients undergoing ablation,(15) there remains uncertainty as to whether these findings are applicable to the broader AF population.

Therefore, the current objective of rhythm control strategies in most patients remains symptom control. Yet, measurement of these vital outcomes remains challenging and are not being routinely collected or reported in the largest repository of clinical trials. Furthermore, “treatment success”, as defined by subsequent AF burden and freedom from recurrence, is poorly correlated to quality of life. Thus, “arrhythmia burden” is not an appropriate surrogate for PROs, and this has limited the interpretation of many AF trials to date – it is not clear that the endpoints most important to patients are measured, and therefore it is difficult to know which interventions are of highest value to them. The use of arrhythmia burden in existing trials is a valuable endpoint for clinicians and researchers, but of little value in understanding hrQoL implications of our interventions, which requires PROs.

These data may also reflect that state of AF clinical research in general. A recent analysis of only interventional AF studies in the clinicaltrials.gov dataset demonstrated some variability in the quality of trials – many only modest in size, and no consistent use of randomization or blinding.(16) Our analysis focuses on an even broader cohort of registered AF studies (all phases, all designs, any status), and these shortcomings appear to extend to a lack of PROs, particularly a lack of AF-specific PROs. This is despite the development and validation of several AF-specific PRO measurement tools (17) that have been studied extensively. Furthermore, there are robust data in support of using AF-specific PRO tools over general hrQoL assessments.(18) Lastly, the latest consensus on AF ablation “… recommends that all clinical trials incorporate some measure of patient reported outcomes and preferably measure them using both a general and an AF specific measurement scale.”(9) More detailed guidance on PRO incorporation in clinical trials has recently been provided by the SPIRIT-PRO group.(19) Nevertheless, our data demonstrate suboptimal implementation of PROs in AF research, according to the clinicaltrials.gov registry.

While the clinicaltrials.gov dataset may be limited and exclude smaller or observational studies that are not required to be registered, it remains the *de facto* registration repository for landmark and regulatory-pathway studies and registration is often required by journals before considering publication of study results. Therefore, the absence of PROs among studies included in this dataset represents an informative, if potentially incomplete, assessment of their use in AF clinical research. As there has been increasing scrutiny on the use of brief duration AF as an endpoint in clinical trials,(20) and since such events are often clinically inconsequential to patients, PROs offer a much better opportunity to demonstrate value of an intervention to patients. Furthermore, optimal and efficient implementation of PROs in studies, both generic and disease-specific, could be greatly enhanced with their routine incorporation into clinical care and the electronic health record.(21,22) This would also facilitate additional, much needed research, such as: (1) identifying minimum clinically important changes in PROs for AF; (2) understanding the correlation between PROs and

more ‘traditional’ outcomes of arrhythmia recurrence, arrhythmia burden, and clinical events (e.g., thromboembolism, heart failure); and (3) using PROs to guide treatment decisions.

Limitations

The data analyzed here are derived from a publicly available registry, where data are entered manually, and often voluntarily, by study personnel. Not all data elements are required (requirements change over time) and many studies are not completed or are completed without results reported; only primary (and not secondary) outcomes are downloaded.(23) Additionally, changes over time in the patterns of trial registration (e.g., study types, etc.) and availability of PROs could influence the assessment of chronological trends. Lastly, responsible persons may not have included PROs in the clinicaltrials.gov registration, even if they were collected. However, this implies that such outcomes were neither (a) the primary outcome, nor (b) felt to be of sufficient import to include in this registry (though may have been identified during our PubMed review). This, in and of itself, reflects an under-emphasis of outcomes that are of primary concern to patients with AF – as technologies rapidly develop to more effectively detect and treat AF, it is incumbent on the field to ensure we are improving outcomes that matter to patients.

Conclusions

Despite increased emphasis on research for AF interventions, a minority of registered AF clinical trials reported the use of PROs as outcomes measures, and very few describe collection of validated, AF-specific PROs. These data reflect an under-emphasis of outcome measures most relevant to patients, and among the most important studies in AF. Improving the care of patients with AF will necessitate increased emphasis on these PROs in the pivotal clinical trials of contemporary interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosure Information

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Perspectives

Competency in Medical Knowledge

Despite recommendations from international governing bodies that patient reported outcomes (PROs) be included in all clinical studies of atrial fibrillation (AF), a minority of trials cite them as primary outcomes in clinicaltrials.gov registrations.

Translational Outlook

While there is contemporary evidence suggesting improvement clinical events and mortality among patients undergoing rhythm control for AF, the primary objective of this approach remains symptom control. However, validated, AF PROs are cited as primary outcomes in a minority of these registered trials. Understanding the impact of interventions on these outcomes that frequently matter most to patients will require greater emphasis and commitment to PROs in clinical studies of AF.

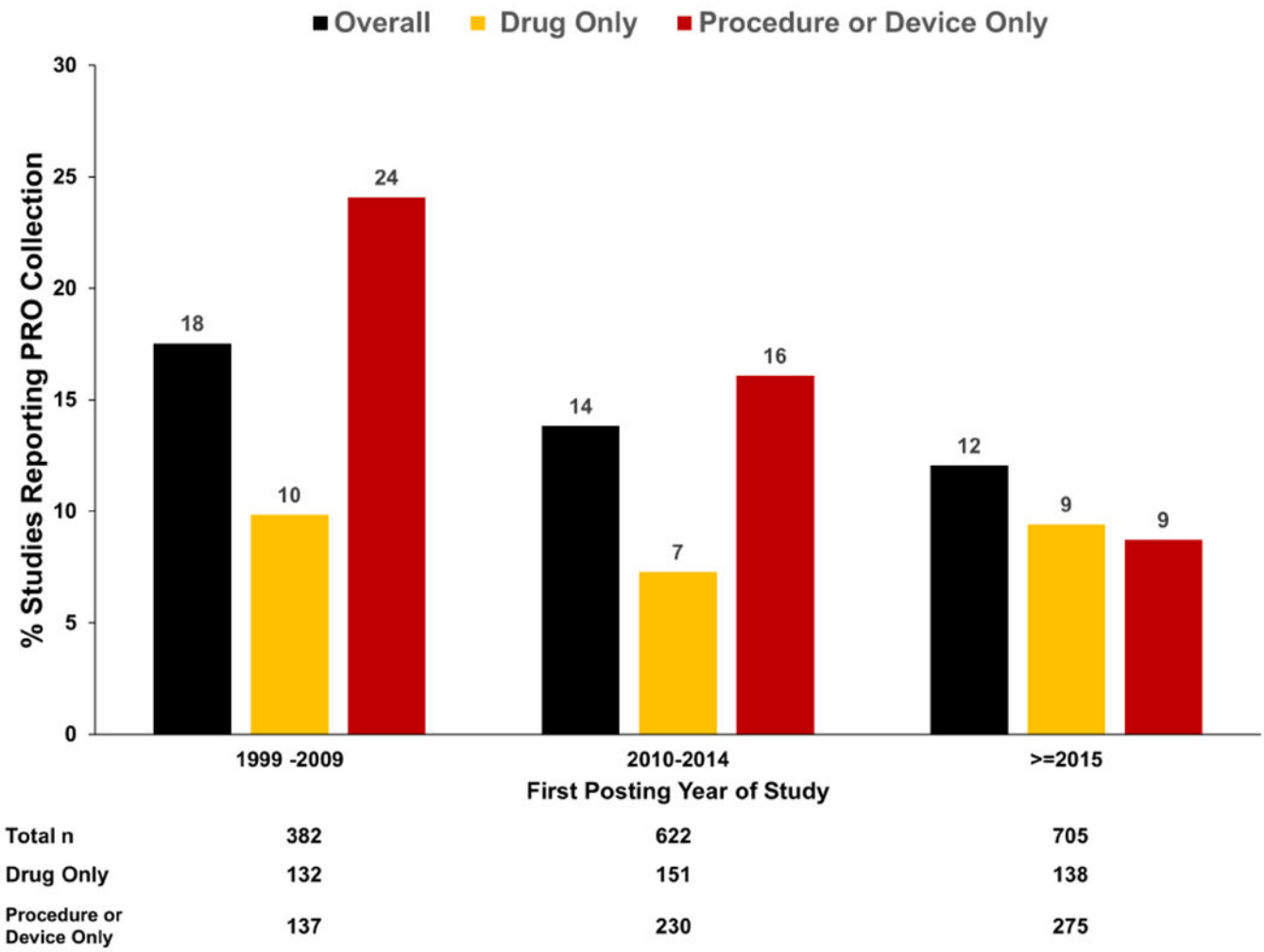
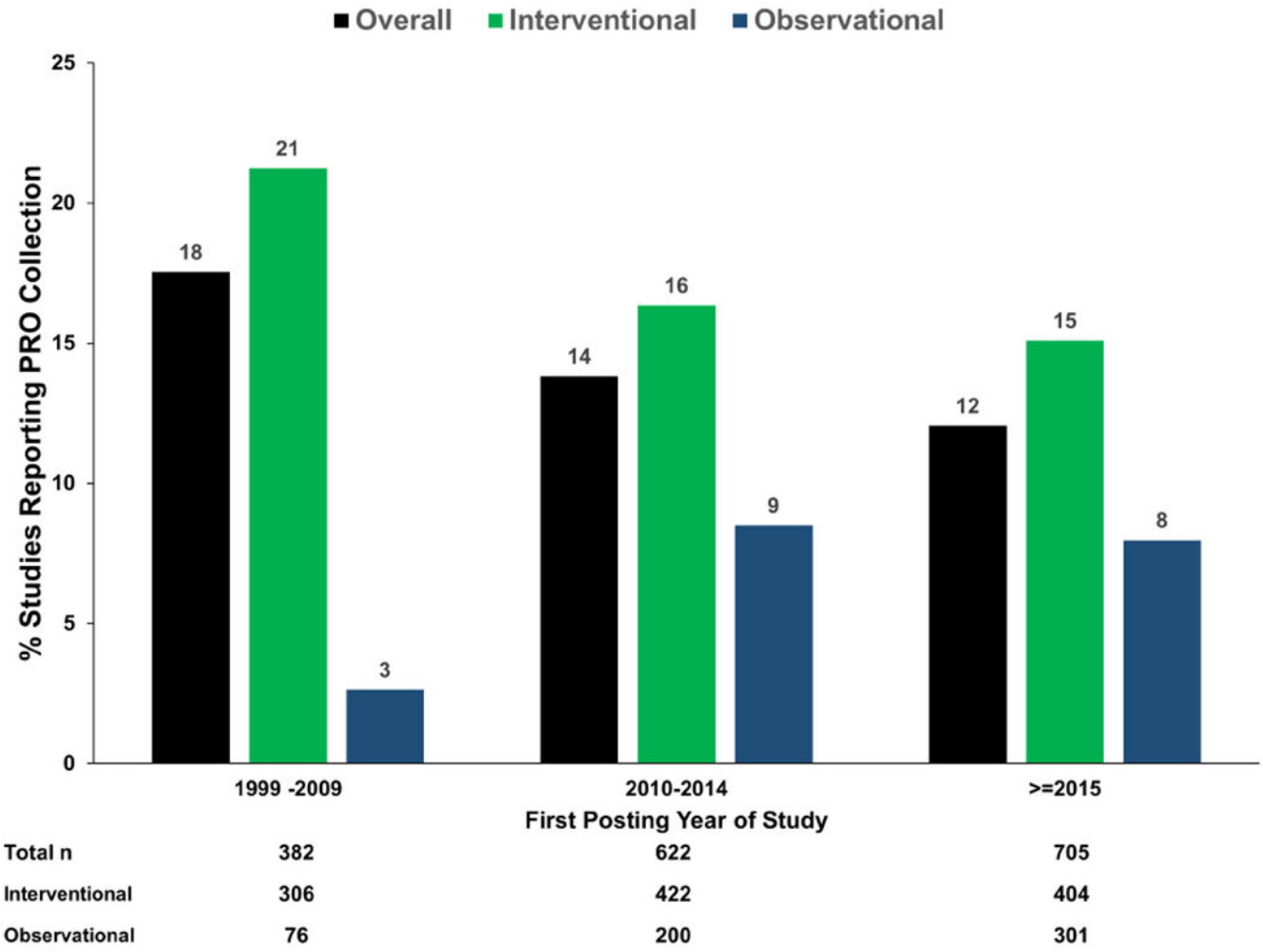


Figure 1.

Trends in reported collection of PROs over time, stratified by reported study type in clinicaltrials.gov.

ROs: patient reported outcomes



Central Illustration.

Trends in reported collection of PROs over time, stratified by reported study intervention type in clinicaltrials.gov. Drug studies include studies that reported only a drug as an intervention; procedure or device studies included procedure, device, or ablation as the intervention (without drug). Studies with other interventions or with both drug and procedure/device interventions were not included in the stratified data (thus the sum does not equal total).

PROs: patient reported outcomes

Table 1.

Characteristics of clinical trials that did and did not include patient reported outcomes.

	Overall (n=1709)	No PROs Reported (n=1471)	PROs Reported (n=238)	p
Study Type (%)				<0.001
Expanded Access	1 (0.1)	1 (0.1)	0 (0.0)	
Interventional	1132 (66.2)	937 (63.7)	195 (81.9)	
Observational	576 (33.7)	533 (36.2)	43 (18.1)	
Year First Posted				0.045
1999 -2009	382 (22.4)	315 (21.4)	67 (28.2)	
2010-2014	622 (36.4)	536 (36.4)	86 (36.1)	
>=2015	705 (41.3)	620 (42.1)	85 (35.7)	
Study Size				<0.001
<100	551 (32.7)	487 (33.7)	64 (26.9)	
100-499	705 (41.8)	587 (40.6)	118 (49.6)	
500-999	128 (7.6)	99 (6.8)	29 (12.2)	
>=1000	301 (17.9)	274 (18.9)	27 (11.3)	
AF Type Included				
Only Paroxysmal	111 (6.5)	91 (6.2)	20 (8.4)	0.252
Paroxysmal	121 (7.1)	101 (6.9)	20 (8.4)	0.471
Persistent	81 (4.7)	70 (4.8)	11 (4.6)	1.000
Permanent	10 (0.6)	8 (0.5)	2 (0.8)	0.922
Not specified	1510 (88.4)	1305 (88.7)	205 (86.1)	0.297
Study Funding				
Industry	683 (40.0)	592 (40.2)	91 (38.2)	0.606
NIH	39 (2.3)	34 (2.3)	5 (2.1)	1.000
Other	1241 (72.6)	1060 (72.1)	181 (76.1)	0.229
Federal Government (US)	15 (0.9)	14 (1.0)	1 (0.4)	0.659
Intervention				
Drug	527 (30.8)	464 (31.5)	63 (26.5)	0.135
Procedure	386 (22.6)	303 (20.6)	83 (34.9)	<0.001
Device	415 (24.3)	363 (24.7)	52 (21.8)	0.388
Behavior	52 (3.0)	32 (2.2)	20 (8.4)	<0.001
Other Intervention	196 (11.5)	153 (10.4)	43 (18.1)	0.001
Ablation	329 (19.3)	253 (17.2)	76 (31.9)	<0.001
Status (%)				0.163
Active, not recruiting	118 (6.9)	98 (6.7)	20 (8.4)	
Completed	735 (43.0)	633 (43.0)	102 (42.9)	
Enrolling by invitation	18 (1.1)	17 (1.2)	1 (0.4)	
No longer available	1 (0.1)	1 (0.1)	0 (0.0)	
Not yet recruiting	85 (5.0)	76 (5.2)	9 (3.8)	
Recruiting	377 (22.1)	321 (21.8)	56 (23.5)	
Suspended	7 (0.4)	4 (0.3)	3 (1.3)	

	Overall (n=1709)	No PROs Reported (n=1471)	PROs Reported (n=238)	p
Terminated	107 (6.3)	88 (6.0)	19 (8.0)	
Unknown status	220 (12.9)	194 (13.2)	26 (10.9)	
Withdrawn	41 (2.4)	39 (2.7)	2 (0.8)	
No Results Available (%)	1534 (89.8)	1312 (89.2)	222 (93.3)	0.070
Phases (%)				<0.001
Early Phase 1	4 (0.4)	4 (0.4)	0 (0.0)	
Not Applicable	590 (52.1)	467 (49.8)	123 (63.1)	
Phase 1	24 (2.1)	22 (2.3)	2 (1.0)	
Phase 1|Phase 2	12 (1.1)	12 (1.3)	0 (0.0)	
Phase 2	96 (8.5)	93 (9.9)	3 (1.5)	
Phase 2|Phase 3	11 (1.0)	10 (1.1)	1 (0.5)	
Phase 3	168 (14.8)	150 (16.0)	18 (9.2)	
Phase 4	227 (20.1)	179 (19.1)	48 (24.6)	

PRO: patient reported outcomes

Characteristics of included studies of atrial fibrillation, as reported by most recent posting.

Values are presented as n (%).

Table 2.

Generic and AF-specific PROs identified as outcomes, among all studies reporting PROs, by study type.

	All Studies Reporting PROs (n=238)	Interventional (n=195)	Observational (n=43)	p
EQ-5D	24 (10.1)	22 (11.3)	2 (4.7)	0.304
“Short-form”	2 (0.8)	2 (0.2)	0 (0.0)	0.793
SF-36	24 (10.1)	22 (11.3)	2 (4.7)	0.304
SF-12	8 (3.4)	6 (3.1)	2 (4.7)	0.959
Quality of Life	194 (81.5)	170 (87.2)	24 (55.8)	<0.001
“Questionnaire”	65 (27.3)	46 (23.6)	19 (44.2)	0.011
“Inventory”	2 (0.8)	0 (0.0)	2 (4.7)	0.036
“Depression”	8 (3.4)	6 (0.5)	2 (0.3)	0.880
PHQ-9	3 (1.3)	3 (1.5)	0 (0.0)	0.949
MLWHF	3 (1.3)	3 (1.5)	0 (0.0)	0.949
DASS	1 (0.4)	1 (0.5)	0 (0.0)	1.000
AF-Specific PROs	40 (16.8)	32 (16.4)	8 (18.6)	0.902
Symptom checklist (SCL)	9 (3.8)	8 (4.1)	1 (2.3)	0.911
AFEQT	20 (8.4)	19 (9.7)	1 (2.3)	0.199
AFSS	7 (2.9)	6 (3.1)	1 (2.3)	1.000
MAFSI	1 (0.4)	1 (0.5)	0 (0.0)	1.000
PACT	5 (2.1)	0 (0.0)	5 (11.6)	<0.001
ASTA	1 (0.4)	1 (0.5)	0 (0.0)	1.000
AF QoL	3 (1.3)	3 (1.5)	0 (0.0)	0.949

Terms reported in the search methods but not reported here did not yield any results.

PROs: patient reported outcomes; AF: atrial fibrillation; SF: Short-Form; PHQ-9: Patient Health Questionnaire; MLWHF: Minnesota Living with Heart Failure questionnaire; AFEQT: Atrial Fibrillation Effect on QualiTy-of-life; AFSS: Atrial fibrillation Symptom Score (University of Toronto); MAFSI: Mayo Atrial Fibrillation Symptom Inventory; PACT: Perception of Anticoagulant Treatment questionnaire; ASTA: Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia.

Table 3.

Description of patient reported outcomes among registered clinical trials of atrial fibrillation that have at least 1 associated PubMed citation.

	Studies With ≥1 Associated PubMed Citation (n=391)
Study Marked 'Completed' in clinicaltrials.org	260 (66.5)
PROs identified in clinicaltrials.org entry	66 (16.9)
AF-specific PROs	6 (1.5)
Generic PROs	65 (16.6)
≥1 full-text manuscript available and accessed from PubMed	375 (95.9)
Rational & Design Citation Available	91 (23.3)
Results Citation Available	333 (85.2)
Collection of PROs Described in Methods	86 (22.0)
Results of PROs Reported	60 (15.3)
Specific PRO Tool Identified	74 (18.9)
AF-specific PROs Tool Identified	29 (7.4)
Any PROs Collected (according to either clinicaltrials.gov or PubMed)	112 (28.6)
AF-Specific PROs Collected (according to either clinicaltrials.gov or PubMed)	31 (7.9)

PROs: patient reported outcomes; AF: atrial fibrillation.