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Early discontinuation and results reporting of robot-assisted surgery studies registered on ClinicalTrials.gov: a research on research study

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ABSTRACT

Objectives In this study, we aimed to investigate the characteristics of robot-assisted surgery studies registered on ClinicalTrials.gov and identify factors associated with early trial discontinuation and timely results reporting.

Design We searched ClinicalTrials.gov to identify interventional studies on robot-assisted surgery on 24 May 2021. All structured information of the potential studies was downloaded and reviewed. A descriptive analysis was performed. Logistic and Cox regression analyses were respectively performed to determine the significance of the association of study characteristics with results reporting and early discontinuation.

Results A total of 529 interventional studies on robot-assisted surgery were included, with 45 studies reporting results and 54 studies being stopped early. Of the 289 due studies, only 45 (16%) had submitted their results, and only 6 (2%) had submitted their results within the 1-year deadline. Funding source was associated with results reporting: academic funded were 63% less likely than industry to report results (OR=0.37, 95% CI: 0.16 to 0.83, p=0.02). Studies related to device feasibility were associated with greater risk of early discontinuation compared to treatment-related studies (HR=2.30, 95% CI: 1.08 to 4.89, p=0.03). Surprisingly, National Institutes of Health-funded studies were at greater hazard of discontinuation compared to industry-funded studies (HR=3.30, 95% CI: 1.09 to 10.00, p=0.04).

Conclusions There was poor compliance with results reporting requirements for robot-assisted surgical studies. It is important that investigators remain informed about the regulatory requirements, and should be helped to develop a sense of responsibility for reporting results. Also, they need to ensure the careful design of the study protocol and adequate resources to reduce the risk of early discontinuation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to comprehensively characterise robot-assisted surgery studies registered in ClinicalTrials.gov, and assess compliance with the Final Rule of the reporting requirements. Our findings facilitated understanding of factors affecting study completion and reporting results, which may be crucial in improving robot-assisted surgery research.
⇒ Although investigators are legally responsible for ensuring their own registry data are accurate and liable according to Food and Drug Administration Amendments Act, data at ClinicalTrials.gov is not guaranteed to be accurate, which is one of the limitations in our study.
⇒ Whether the enrolment used in each study is actual or planned is difficult to ascertain, but this did not influence the main findings.

INTRODUCTION

In recent decades, the number of robot-assisted surgery interventions has increased exponentially, achievihng 570 000 cases in 2014 for the da Vinci surgical system.[1] The use of robots had an increase of 13% (about US$3200) on the average total cost of a procedure in 2007 for 20 different robot-assisted surgery interventions.[2 3] Robot-assisted surgery has become more and more widely applied in surgical specialties, and massive clinical studies were triggered.[4] A large number of observational studies and randomised controlled trials costing a lot of human, physical and financial resources[5] compared robot-assisted surgery with laparoscopic surgery, video-assisted surgery or open surgery, but the results have been inconsistent.[6]

Because unreported trials represent a human rights violation, researchers have a potential obligation to make research results publicly available, particularly findings of human clinical trials.[7 8] Nevertheless, plenty of examples exist of selective non-publication of trials with negative results or potentially harmful findings, especially those that were stopped early or with severe adverse effects, and publication bias (negative results are less likely to be published than positive results).[9–11]

ClinicalTrials.gov is a study registration system developed for greater transparency and less risk of bias. Certain interventional trials listed there are required to report results within 1 year of the primary completion date, according to the Food and Drug Administration Amendments Act (FDAAA) of 2007.[12 13] By September 2016, the National Institutes of Health (NIH) and the Department of Health and Human Services expanded mandatory reporting of results to the ClinicalTrials.gov in the Final Rule.[14] A lack of timely dissemination of research findings may influence clinical practice, have major effects on the development of evidence-based clinical policies and even have the potential for a large impact on public health.[15] Those resources will not go to waste only when clinical trial findings can foster scientific advances.[16 17]

The rapid growth in the number of robot-assisted surgery research coupled with the major investments of trial resources compounds the need for ensuring trials complete and dissemination of results and is still a crucial issue in the field of robot-assisted surgery. Therefore, we aimed to investigate the characteristics of robot-assisted surgery studies registered on ClinicalTrials.gov and identify factors associated with early trial discontinuation and timely results reporting.

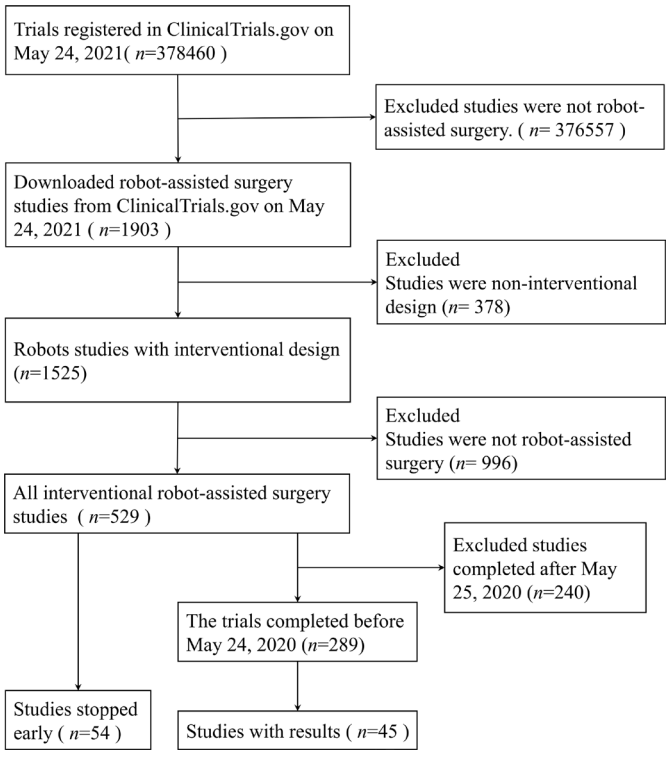

Figure 1 Flow chart of robot-assisted surgery studies.

MATERIALS AND METHODS

Search strategy and data selection

We searched ClinicalTrials.gov to identify interventional studies on robot-assisted surgery on 25 May 2021, using the search terms including robot OR robotic OR robotics OR robot-assisted. All structured information of the potential studies was downloaded. Two researchers independently reviewed the full study records on ClinicalTrials.gov to include interventional studies relevant to robot-assisted surgery focused on effect and safety. Any disagreements were resolved by a third researcher.

Data extraction and classification

The following information was collected: NCT number, study title, specialty, primary purpose, status, study results, interventions, phase, study design, enrolment, collaborator, funder type, start date, primary completion date and first posted date of results. The specialties of studies were classified as gastroenterology, general, gynaecology, head and neck, orthopaedics, urology or others. Additionally, the classification method of the funder is essentially identical to previously published methods.[5 18]

Data analysis

We calculated the time from the study start date to the primary completion date. Categorical variables were summarised as numbers and percentages. The Kaplan-Meier method was used to calculate the cumulative incidence of results reporting in studies with reported results and early discontinuation in studies early stopped. We performed logistic regression analyses to explore the association of study characteristics (primary purpose, intervention model, blinding and funder type) with results reporting. For early discontinuation, the duration of studies also required consideration because of its potential association with a waste of resources. We; therefore, chose Cox regression analyses for early discontinuation. Considering only studies in the completion status requiring reporting results, we limited to interventional studies completed before 25 May 2020 (the year prior to searching the Clinicaltrials.gov) in the logistic regression, following the FDAAA of 2007.[12] The statistical analysis was performed with Stata V.15.0 software, with test results considered statistically significant for two-tailed p values of <0.05.

Patient and public involvement

None.

RESULTS

We identified 1903 registered studies from 378 460 registered studies, 529 of which met inclusion criteria, including 289 (54.6%) studies completed before 24 May 2020 (figure 1).

General characteristics

The trial characteristics are summarised in table 1. Among the 529 included studies, the specialties with the highest number were urology (145, 27.4%) followed by gastroenterology (115, 21.7%). In 398 (75.2%) of the studies on robot-assisted surgery, the primary purpose was treatment. A total of 170 trials (32.1%) had been completed, 235 (44.4%) were ongoing, 54 (10.2%) were stopped early and 45 (8.5%) had results. The

Table 1 Characteristics of robot-assisted surgery studies registered on ClinicalTrials.gov

Characteristics	N=529, n (%)
Specialty	
Urology	145 (27.4)
Gastroenterology	115 (21.7)
Gynaecology	76 (14.4)
Head and neck	54 (10.2)
Orthopaedics	54 (10.2)
General	41 (7.8)
Other	44 (8.3)
Primary purpose	
Treatment	398 (75.2)
Device feasibility	60 (11.3)
Other	71 (13.4)
Status	
Ongoing	235 (44.4)
Completed	170 (32.1)
Unknown	70 (13.2)
Discontinue early	54 (10.2)
Study results	
No	484 (91.5)
Yes	45 (8.5)
Intervention type*	
Procedure	290 (54.8)
Device	153 (28.9)
Drug	52 (9.8)
Other	96 (18.1)
Phase	
Early phase 1	6 (1.1)
Phase 1	11 (2.1)
Phase 1 and phase 2	7 (1.3)
Phase 2	28 (5.3)
Phase 2 and phase 3	3 (0.6)
Phase 3	28 (5.3)
Phase 4	27 (5.1)
Not applicable	419 (79.2)
Randomised	
Yes	321 (60.7)
No	59 (11.2)
Not reported	149 (28.2)
Blinding	
None	332 (62.8)
Single	100 (18.9)
Double	43 (8.1)
Triple	32 (6.0)
Quadruple	19 (3.6)
Not reported	3 (0.6)
Intervention model	
Crossover assignment	6 (1.1)
Factorial assignment	4 (0.8)
Not reported	2 (0.4)
Parallel assignment	345 (65.2)
Sequential assignment	6 (1.1)
Single group assignment	166 (31.4)
Enrolment	
0–9	53 (10.0)
10–49	135 (25.5)
50–99	123 (23.3)
100–499	186 (35.2)
500–999	20 (3.8)
≥1000	12 (2.3)
Start year	
Before 2011	54 (10.2)
2011–2015	150 (28.3)
2016–2020	286 (54.1)
After 2020	39 (7.4)
Completion year	
Before 2011	13 (2.5)
2011–2015	94 (17.8)
2016–2020	178 (33.6)
After 2020	9 (1.7)
Ongoing	235 (44.4)
During (months)	
0–24	174 (60.2)
25–48	73 (25.3)
≥49	42 (14.5)
Collaborators	
Industry	32 (11.1)
Academic institution	254 (88.2)
Government	2 (0.7)
Funded-by	
Industry	89 (16.8)
Academic institution	416 (78.6)
NIH	24 (4.5)

*A study may have >1 intervention type.
NIH, National Institutes of Health.

traditional study phase was not applicable for the most studies (419, 79.2%). As for study design, 321 (60.7%) was randomised, but only 194 (36.7%) studies used the blinding method. More than half (58.8%) enrolled 100 or fewer participants and 174 studies (60.2%) had a

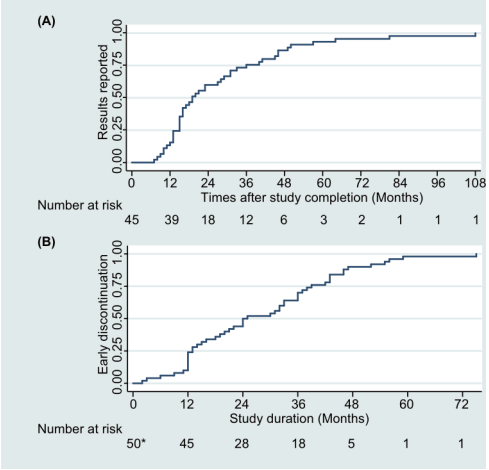

Figure 2 Cumulative incidence of early discontinuation in studies early stopped, and results reporting in studies with reported results. * The other 4 studies in 54 studies early stopped were with 0-month duration.

duration of less than 2 years. Additionally, 89 (16.8%) studies were funded by industry and 24 studies were funded by (4.5%) by NIH.

Results reporting

For 289 studies completed before 24 May 2020, 45 (15.6%) reported results. In these 45 studies with reported results, the proportion of studies reporting results increased over time after primary completion, with reporting rates of 13.3% at 12 months, 60.0% at 24 months, 73.3% at 36 months, 86.7% at 48 months and 93.3% at 60 months (figure 2A). Univariate logistic regression analysis showed industry funded and NIH funded had comparable reporting, but studies funded-by academic institutions were less likely to report results (OR=0.36, 95% CI: 0.17 to 0.77, p=0.01) (figure 3). After adjustment for other characteristics, funding source was also associated with results reporting: academic-funded were 63% less likely than industry to report results (OR=0.37, 95% CI: 0.16 to 0.83, p=0.02).

Early discontinuation

The cumulative incidence of early discontinuation in studies early stopped was presented in figure 2B, with rates of 16.7% at 12 months, 48.1% at 24 months, 66.7% at 36 months and 90.7% at 48 months (figure 2B). The proportion of reasons for early discontinuation was greatest for difficulty in recruiting participants (17/54), followed by lack of funding (10/54), protocol change (7/54) and staff shortage (7/54) (online supplemental appendix table 1). Primary purpose (HR=2.59, 95% CI: 1.24 to 5.43, p=0.01), intervention model (HR=1.86, 95% CI: 1.07 to 3.26, p=0.03) and funding source (HR=3.44, 95% CI: 1.14 to 10.34, p=0.03) had significant unadjusted differences on Cox regression analysis (figure 4). After adjustment, studies related to device feasibility were associated with greater risk of early discontinuation compared with treatment-related studies (HR=2.30, 95% CI: 1.08 to 4.89, p=0.03). Surprisingly, NIH-funded studies were at greater hazard of discontinuation compared with industry-funded studies (HR=3.30, 95% CI: 1.09 to 10.00, p=0.04), and industry-funded and academic-funded had comparable discontinuation.

DISCUSSION

The Final Rule of reporting requirements has been ignored largely by researchers in robot-assisted surgery. Of the 289 due studies, only 45 (16%) had submitted their results, and only 6 (2%) had submitted their results within the 1-year deadline. The lack of timely reporting of results was also problematic, with 3 studies results not being reported until 5 years after primary completion among 45 studies that reported results. Industry and NIH funders were more likely to report results, while studies funded by academic institutions had the lowest compliance of any funder type. Additionally, about 10% of the robot-assisted surgery studies were discontinued early, and the main cause for this was the difficulty of recruiting participants, lack of funding, protocol change and staff shortage. We also found primary purpose, and funding

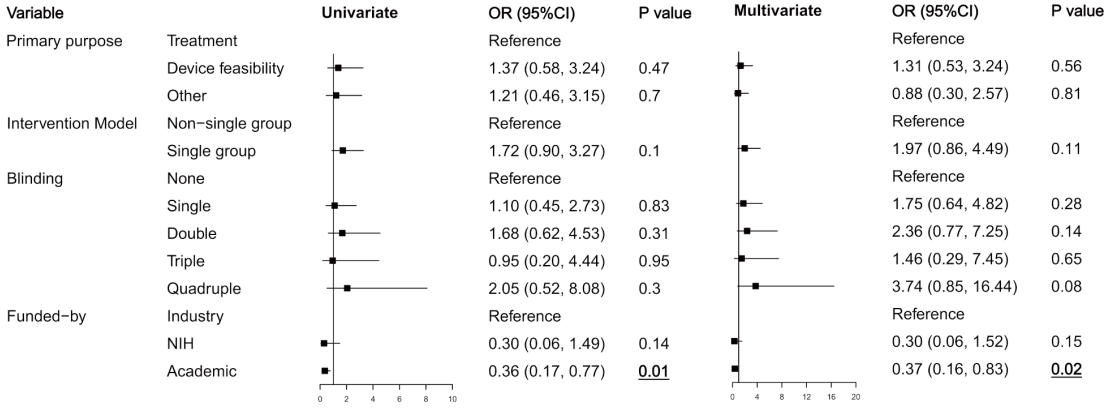

Figure 3 Association of characteristics with results reported in completed robot-assisted surgery trials. NIH, National Institutes of Health.

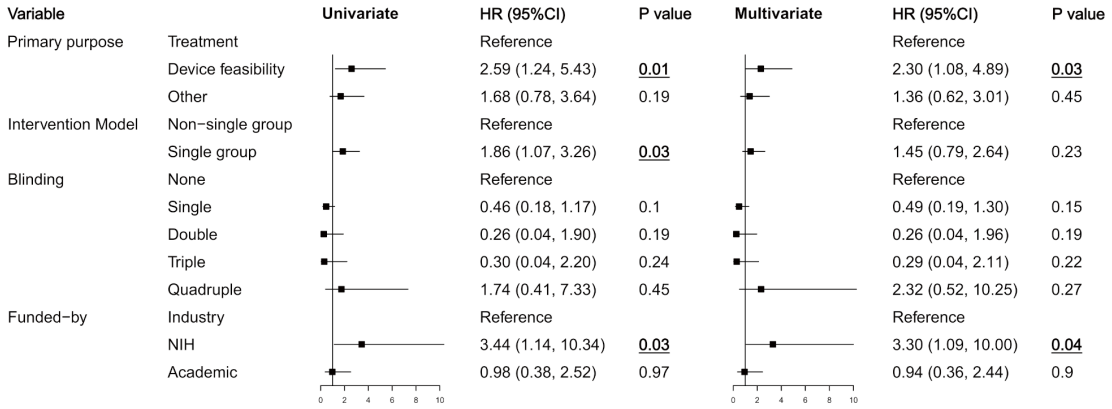

Figure 4 Association of characteristics with early discontinuation in robot-assisted surgery trials. NIH, National Institutes of Health.

source to be significant independent predictors of early discontinuation.

Generally, clinical studies on robot-assisted surgery are expensive, practical evaluations that aim to directly inform clinical practice. The lack of study data hampers the systematic review process and the development of guidelines, results in patients and clinicians not being able to make informed decisions and influencing the process of incorporating the robotic devices into medical insurance.[15] It has been emphasised since the 1980s that the bias from non-publication of clinical studies is significant. However, the results reporting mechanism designed to improve publication bias is still largely ignored. Thus, researchers need to be held responsible for reporting their results and the management of mandatory results reporting needs to be strengthened. The positive association with industry funding illustrates the potential effects of funding sources on results reporting. Academic-funded studies had negative association with results reporting, possibly reflecting limited resources or the lack of experience.

According to DeVito *et al*, the percentage of compliant studies (submitting their results to the ClinicalTrials.gov) has remained at about 40% since July 2018.[12] In some specific fields (such as neurology and late-stage cardiovascular trials), the overall results reporting rates were within the range of 22%–41%.[5 12 19–23] Again, the results reporting rates within 1 year of primary completion in the previous studies were within the range of 13%–15%.[14 19] These proportions are higher than results from our current study on robot-assisted surgery, and this may relate to different national requirements or incentives for timely dissemination in a registry.[12] The lower percentage of compliant studies on robot-assisted surgery raises concerns that positive results may be more common in published studies and thus overestimate the overall efficacy. Additionally, our results corroborate past reports indicative of academic-funded studies having the lowest odds of results reporting.[5 7 14] Kapelios *et al*[24] and Roddick *et al*[21] found that industry-sponsored studies were more likely to report results, which is consistent with our results.

Turner *et al* found 11.3% of neurology trials were discontinued early, and the results of Cox regression of early discontinuation showed both academic and government-funded trials had a greater risk of discontinuation than industry (adjusted hazard 0.57 and 0.46, respectively).[5] Bernardez-Pereira *et al*[20] found 10.9% were terminated prematurely in 6279 cardiovascular trials registered in ClinicalTrials.gov, but the results demonstrated that academic-funded (OR 1.52, 95% CI 1.10 to 2.10) were associated with a higher likelihood of early termination due to lower than expected recruitment rates. Those discontinuation rates are similar to those presented in our study. Surprisingly, our findings suggest that NIH-funded studies were more likely to discontinue early, which was somewhat inconsistent with previous studies. This could be relevant for more changes in the protocol and staff in NIH-funded studies. However, the underlying reasons remain to be further explored.

Our study has several limitations. First, data at ClinicalTrials.gov is not guaranteed to be accurate.[25] Usefully, investigators are legally responsible for ensuring their own registry data are accurate and liable according to FDAAA.[12] In addition, we did not search other study registration databases, but we believed that our results were still conservative, because clinicaltrials.gov is the largest one of these databases[15] and was developed by the US National Library of Medicine. Second, whether the enrolment used in each study is actual or planned is difficult to ascertain, but this did not influence the main findings. Third, because of the small sample for most specialties, we have not pursued this further. Finally, whereas not all studies are legally obligated to disseminate findings, submitting results should be recommended as a best practice to support appropriate clinical decisions.

To the best of our knowledge, this is the first study to comprehensively characterise robot-assisted surgery studies registered in ClinicalTrials.gov, and assess compliance with the Final Rule of the reporting requirements. In general, our findings facilitated understanding of factors affecting study completion and reporting results which may be crucial in improving robot-assisted surgery research. First, investigators focused on robot-assisted

surgery must value the reporting of results and its timeliness, and view it as a key link in the scientific research regardless of negative results, making it more possible to assess the true clinical value and cost-effectiveness of the robot-assisted surgery. Second, the fact that studies funded by industry had a relatively low hazard of early discontinuation and a high rate of results reporting supports the positive impact of increased resources in robot-assisted surgery research. Poor funding and lack of resources are easier to lead to failed trials in the robotic-assisted surgery field because surgical robotic systems are quite expensive. Third, careful trial design and implementation that can reduce the risk of protocol change could aid in greater trials success.[5]

There was poor compliance with results reporting requirements for robot-assisted surgical studies. It is important that investigators remain informed about the regulatory requirements, and should be helped to develop a sense of responsibility for reporting results. Also, they need to ensure the careful design of the study protocol and adequate resources to reduce the risk of early discontinuation.

Contributors YL: conceptualisation, methodology, data curation, formal analysis, writing—original draft, writing—review and editing. TH: conceptualisation, methodology, data curation, formal analysis. ZY: data curation, formal analysis. LL: data curation, formal analysis. YL: data curation. JH: formal analysis, writing—review and editing. LD: conceptualisation, methodology, formal analysis, writing—review and editing. LD is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The ethics approval is not applicable for this study because it is a research on research study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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