

# Availability of Results of Trials Studying Pancreatic Adenocarcinoma over the Past 10 Years

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## Abstract

**Background:** Pancreatic adenocarcinoma (PDAC) is a lethal cancer with few therapeutic options. Availability of results is a crucial step in interventional research. Our aim was to evaluate results availability for trials in patients with PDAC and explore associated factors.

**Materials and Methods:** We performed a retrospective cohort study and searched the ClinicalTrials.gov registry for trials evaluating PDAC management with a primary completion date between 1 January 2010 and 1 June 2020. Then, we searched for results submitted on ClinicalTrials.gov and/or published. Our primary outcome was the proportion of PDAC trials with available results: submitted on ClinicalTrials.gov (either publicly available or undergoing quality control check) and/or published in a full-text article. The association of predefined trial characteristics with results availability was assessed.

**Results:** We identified 551 trials of which 386 (70%) had available results. The cumulative percentage of trials with available results was 21% (95% CI, 18–25%) at 12 months after the primary completion date, 44% (95% CI, 30–48%) at 24 months and 57% (95% CI, 53–61%) at 36 months. Applicable clinical trials, required to comply with the 2007 Food and Drug Administration Amendments Act 801 and its final rule on reporting of results on ClinicalTrials.gov, were more likely to have available results over time (HR 2.1 [95% CI 1.72–2.63],  $P < .001$ ). Industry-funded, small sample size, and terminated trials were less likely to have available results. Other trial characteristics showed no association with results availability.

**Conclusion:** Our results highlight a waste in interventional research studying PDAC.

**Key words:** interventional research; pancreatic adenocarcinoma; ClinicalTrials.gov; results availability; FDAAA 801.

## Implications for Practice

This work is the first to assess results availability in interventional studies evaluating pancreatic adenocarcinoma management and shows that 30% of trials do not have available results over time. Unavailable results in interventional research are an important issue that can impact the development of future therapeutic guidelines and clinical decisions. Pancreatic adenocarcinoma shows a growing incidence and will become an important cancer in Western countries in the near future. It is important for all physicians who will be involved in patient care to know about the waste in research in this field.

## Introduction

Cancer is currently an important public health issue worldwide. Pancreatic cancer, mostly represented by pancreatic adenocarcinoma (PDAC), is the 11th most common cancer and the seventh cause of cancer-related deaths worldwide.<sup>1</sup> Its incidence has been rising in the past years, especially in Western countries.<sup>1–3</sup> Despite the development of various treatments, the prognosis remains very low with a 5-year survival rate of about 10% and approximately 432 242 deaths registered in 2018.<sup>1</sup> New therapeutics for PDAC are urgently needed.

Lately, there has been an increased rate of trials conducted in the oncology field with a growing number of pilot and industry-sponsored trials.<sup>4,5</sup> Various works have highlighted

an important waste in the production and reporting of research because of the lack of quality and standardization in the different research steps.<sup>6–8</sup> Availability of results is a crucial step<sup>9–11</sup> to prevent the risk of biased literature which can negatively impact future meta-analyses results and the development of therapeutic guidelines.<sup>12,13</sup> Also, not publishing trial results raises an ethical issue for patients who agree to participate in these trials.

For a better monitoring of the new research, it has been recommended since 2004 to register all clinical trials on a registry.<sup>14,15</sup> Various registries such as ClinicalTrials.gov, developed by the United States (US) National Institutes of Health (NIH), and EudraCT, the European registry, require the reporting of most trial results on the registry. Since 2007, the US Food and

Drug Administration Amendments Act 801 (FDAAA 801) has defined applicable clinical trials which are required to submit results on ClinicalTrials.gov no later than one year after the primary completion date, independently of publication in journals. A revision of this act, named the final rule, was implemented on 18 January 2017.

The aim of our work was to assess the availability of trial results and explore associated factors for interventional studies registered on ClinicalTrials.gov and evaluating PDAC management over the past 10 years.

## Methods

### Search Strategy

We searched the US National Library of Medicine database of clinical trials, ClinicalTrials.gov, on 1 July 2021, for all interventional studies, completed or terminated between 01 January 2010 and 01 June 2020, and evaluating PDAC management in adults ([Supplementary Table S1](#). Advanced search on ClinicalTrials.gov).

### Data Extraction

We downloaded the list of trials encountered with our previous search, all referenced on ClinicalTrials.gov with a unique identification NCT number. Based on this NCT number, we then extracted a selection of items from the Clinical Trials Transformation Initiative (AACT database) which is a publicly available relational database containing all information about every study registered on ClinicalTrials.gov. To do so, we used the Beaver software (SQL language). The selected extracted items are listed in our data extraction form ([Supplementary Table S2](#)).

### Sample Identification: Inclusion and Exclusion Criteria

Inclusion criteria were: all completed or terminated interventional studies, performed in adults, of any phase and any size of enrollment, focusing on PDAC management, and with a primary completion date between 01 January 2001 and 01 June 2020. We defined as “management”, all trials focusing on screening, diagnosis, prevention (secondary and tertiary), treatment (including drugs, biological products, dietary supplements, behavioral interventions, devices, radiotherapy, and surgery), and supportive care.

As defined on ClinicalTrials.gov on 01 July 2021, the primary completion date was the date on which the last participant in the study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated did not affect this date. For trials with more than one primary outcome measure, this term refers to the date on which data collection is completed for all the primary outcome measures. The estimated enrollment number was defined as the target number of participants that the researchers need for the study whereas the actual number of enrollment was defined as the final number of patients included in the study.

We then excluded trials focusing on different conditions than PDAC (eg, mixed malignancies, pancreatic neuroendocrine tumors). The identification of our sample of trials was done by one reviewer.

### Identification of Results Availability

For our sample of trials, we systematically searched for results submitted on the ClinicalTrials.gov registry and/or published online in a full-text article.

### Search Strategy for Results

We first identified all included trials with results submitted on the ClinicalTrials.gov registry. Submitted results were defined as either publicly available (posted) or undergoing quality control check at ClinicalTrials.gov. If there were no results submitted on the registry, we assessed if the responsible party had submitted a certification asking for delayed reporting.

We also searched for online publication of results for all included trials, even when results were submitted on the registry, to identify the earliest date of results availability. If more than one publication was identified for one trial, we kept the earliest date of publication. First, we used the publication link on ClinicalTrials.gov when available and posted (direct access to publication). If a publication of results was found with the link, the search was stopped. In the absence of a link on the registry, we searched MEDLINE via PubMed and Google Scholar using keywords for treatment and/or drug names, the principal investigator's last name and the condition studied. If necessary, for industry-funded trials, we also searched the sponsor's website via Google to look for the final results by using the same keywords. All trials without available results were censored on 29 September 2021.

### Eligibility Criteria for Publication of Results

We only considered publications stating they were reporting the main trial results, as defined on the registry. All identified online publications were first assessed by one reviewer who determined if (1) the corresponding study matched in terms of the registered information (ie, same NCT when available, similar title, same studied condition, same interventions, same population, same study location, same authors, and same time period) and (2) reported results in a full-text article. Cases of partial matching were discussed with a senior reviewer.

### Trial Characteristics Evaluated for Association with Results Availability and Submission on the Registry

#### Trial Characteristics

To examine the association of trial characteristics with the availability of results and submission on the registry, we *a priori* selected explanatory variables. The following variables were selected based on their interest: trial status (terminated or completed), trial funding (industry funding, mix funding, or non-industry funding), trial phase (early phase I, phase I, phase I/II, phase II, phase II/III, phase III, phase IV or non-available), trial design (randomized or non-randomized), sample size of enrollment, and applicability according to the 2007 FDAAA 801 and its 2017 final rule. All variables could be directly extracted from the AACT database, except for applicability according to the 2007 FDAAA 801 and its 2017 final rule (see next paragraph).

### Identification of Applicable Clinical Trials Covered by the 2007 FDAAA 801 and the 2017 Final Rule

The definition for applicability has been clarified and updated in the final rule document.<sup>16</sup> Based on their start date, clinical trials are either defined as applicable clinical trials, probable applicable trials, or non-applicable clinical trials.

To classify trials in our sample with the available data extracted, we followed the methodology described by DeVito et al.<sup>17</sup> Applicable clinical trials were identified in our sample using the following criteria: clinical trials with a study start date on or after 18 January 2017 (final rule), studying a US-FDA regulated drug, biological product, or medical device manufactured in and exported from the US, with at least one trial site in the US. Probable applicable clinical trials were identified using the following criteria: clinical trials that started before 18 January 2017 (final rule) and (1) studying an FDA-regulated drug, biological product, or device, or if the information on regulation is lacking, (2) clinical trials studying a drug, biological product (including vaccine and genetic), radiation, medical device, combination product, or diagnostic test, with at least one trial site in the US.

Of note, all registered trials not mentioning the study phase were considered as covered by the 2007 FDAAA 801 if other criteria were fulfilled. Based on our initial search, all trials were initiated after 27 September 2007 or are still ongoing on the 26 December 2007, as implied by the 2007 FDAAA 801.

For more clarity, all trials identified with these two previous definitions will now be referred to as applicable clinical trials.

The rest of the trials in our sample, including early phase I and phase I trials, or trials with a device feasibility purpose or studying behavioral interventions, dietary supplement, or procedures/devices (eg surgery) were identified as non-applicable.

Categorization of applicability was established and validated with a senior reviewer, and identification of applicable clinical trials was done by one reviewer.

## Outcome Measures

### Primary Outcome Measure

Our primary outcome measure was the proportion of included PDAC trials with available results (ie, submitted on the ClinicalTrials.gov registry and/or published in a full-text article).

### Secondary Outcome Measure

The cumulative percentage of included trials with results available at one, two, and three years after the primary completion date.

The cumulative percentage of included trials with results published in full-text articles at one, two, and three years after the primary completion date.

The cumulative percentage of included trials submitting results on the ClinicalTrials.gov registry at one, two, and three years after the primary completion date.

### Statistical Analysis

All statistical analyses were conducted using the R software (R Version 4.0.2). For the assessment of cumulative percentages and time to event analysis, we used the Kaplan–Meier method (survival package in R). If the date of publication of results was anterior to the primary completion date (negative delay for survival), we considered that results were published on the date of trial completion.

To evaluate the association of trial characteristics with results availability and submission of results on the registry over time, we estimated the hazard ratios (HR) in multivariable analysis by using the Cox Proportional-Hazards model. We tested the proportional hazard assumption for each variable in our model by using the cox.zph function on R and plotting the scaled Schoenfeld residuals against time. All

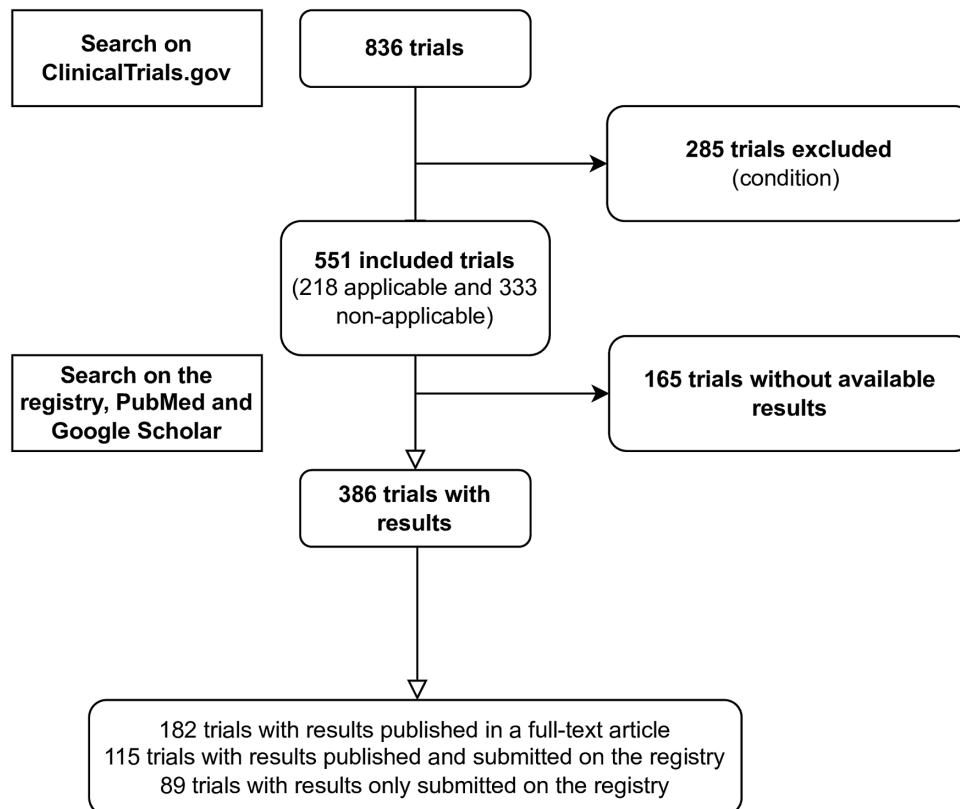


Figure 1. Flow chart of our search.

**Table 1.** General characteristics of the included trials (N = 551).

Characteristics of trials	N (%)
Status	
Terminated	129 (23)
Completed	422 (77)
Study allocation	
Randomized	194 (35)
Non-randomized	357 (65)
Study design	
Single-arm	315 (57)
Parallel	218 (40)
Other <sup>a</sup>	12 (2)
NA	6 (1)
Primary purpose	
Treatment	466 (85)
Diagnostic	54 (10)
Other <sup>b</sup>	31 (5)
Study phase	
Early phase I and phase I	129 (23)
Phase I/II and phase II	279 (51)
Phase II/III, phase III	36 (7)
Phase IV	7 (1)
NA	100 (18)
Trial location	
At least one site in the US	347 (63)
No site in the US or NA	204 (37)
Enrollment type	
Actual	527 (96)
Estimated or NA	24 (4)
Type of funding	
Industry	112 (20)
Mixed	96 (18)
Non-industry	343 (62)
Article link posted on the registry	
Yes	148 (27)
No	403 (73)
Applicability according to the 2007 FDAAA 801 and its 2017 final rule	
Applicable clinical trials	218(40)
Non-applicable clinical trials	333(60)

<sup>a</sup>Other includes crossover, factorial and sequential assignments;

<sup>b</sup>Other includes screening, prevention, and supportive care.

Abbreviations: N: number; NA: non-available;

predefined variables were included in the final analysis. All *P* values were 2-sided, and point estimates were presented with 95% confidence intervals (CIs). The significance level was set at *P* = .05 for all analyses.

## Results

### Sample of Included Trials

Our search on ClinicalTrials.gov found 836 trials of which 551 were included for analysis (Fig. 1). Among these 551 trials, which involved 36 436 patients, 422 (77%) were completed and 466 (85%) had a treatment purpose (Table 1). Most trials with a treatment purpose studied a drug or biological product

(405/466 = 87%). There were 194 (35%) randomized trials, and 129 (23%) early or phase I trials. Most trials used a single-arm design (315, 57%) or parallel design (218, 40%) and were open-labelled (470, 85%). The median size of enrollment was 32 (IQ 13-69), with 527 (96%) trials mentioning the actual number of enrollment. There were 343 (62%) trials non-funded by the industry. In our sample of included trials, we identified 218 applicable clinical trials (including 209 probable applicable clinical trials) and 333 non-applicable clinical trials. Finally, 284 (51%) trials were prospectively registered (registered before the study start date).

### Outcome Results

#### Proportion of Included Trials with Available Results (Primary Outcome Measure)

Among the 551 included trials, 386 (70%) had available results (ie, submitted on the ClinicalTrials.gov registry and/or published in a full-text article). A total of 6273 (17%) patients were involved in trials without results. Of note, 325 trials with a treatment purpose had available results (325/466 = 70%).

Among the 386 (70%) trials with results, 182 (182/386 = 47%) had results solely published in a full-text article, 115 (30%) had results submitted on the registry and published and 89 (23%) had results only submitted on the registry (Fig. 1).

#### Secondary Outcome Measure

Of note, 45 trials had results available before the declared primary completion date.

The cumulative percentage of included trials with available results over time (submitted on the registry and/or published in a full-text article) is shown in Fig. 2 and was 21% (95% CI, 18-25%) at 12 months, 44% (95% CI, 30-48%) at 24 months and 57% (95% CI, 53-61%) at 36 months after the primary completion date. Overall, the median time between the primary completion date and earliest date of results availability was 29.2 months (95% CI, 26.1-33.8) (Fig. 2).

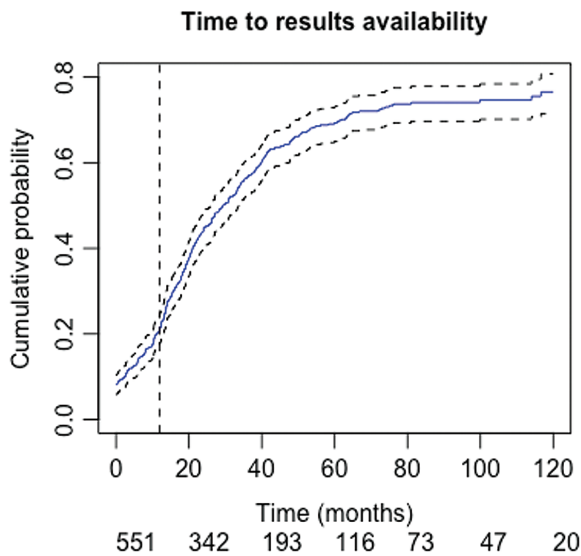
The cumulative percentage of included trials with results published in a full-text article over time is shown in Fig. 3 and was 16% (95% CI, 13-19%) at 12 months, 31% (95% CI, 27-36%) at 24 months and 42% (95% CI, 38-46%) at 36 months after the primary completion date. Overall, for the 297 trials with results available in a full-text article, the median time between primary completion date and date of publication was 47.6 months (95% CI 39.6-61.9) (Fig. 3). Full-text articles were openly accessible from our institution in 278 (278/297 = 94%) of cases.

The cumulative percentage of included trials submitting results on the ClinicalTrials.gov registry is shown in Fig. 4 and was 4% (95% CI, 2-6%) at 12 months, 18% (95% CI, 15-21%) at 24 months and 25% (95% CI, 21-29%) at 36 months after the primary completion date. Overall, the median time between the primary completion date and the earliest date of posting on the registry was 136 months (95% CI, 123-Non-assessable) (Fig. 4).

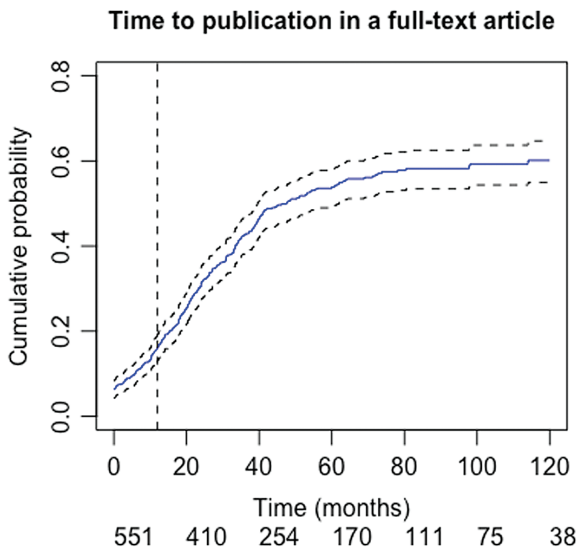
#### Association with Trial Characteristics

Compared to non-industry funded trials, industry, and mixed-funded trials were less likely to have available results (Table 2). Terminated and small sample size trials were less likely to have available results (Table 2). Applicable clinical trials were





**Figure 2.** Cumulative probability of trials with results available over time. The dotted curves represent the 95% confidence intervals. The vertical dotted line represents the 12 months cut-off.



**Figure 3.** Cumulative probability of trials with results published in full-text articles over time. The dotted curves represent the 95% confidence intervals. The vertical dotted line represents the 12 months cut-off.

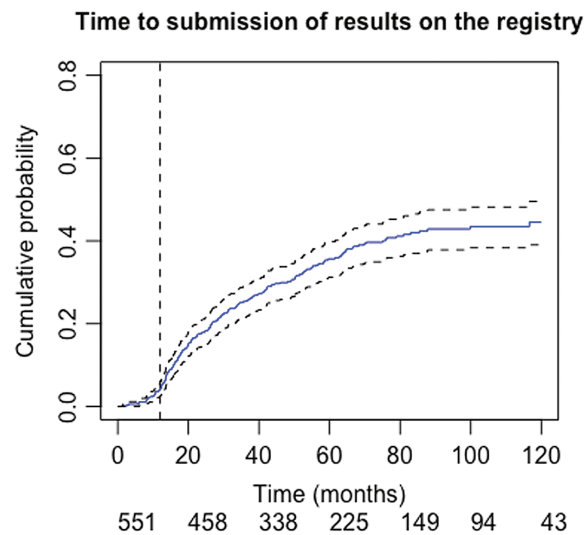
more likely to have available results (HR = 2.13 [95% CI, 1.73-2.63],  $P < .001$ ) (Table 2).

Applicable clinical trials were also more likely to submit results on the registry (HR = 13.37 [95% CI, 9.24-19.36],  $P < .001$ ) (Table 2). Other trial characteristics were not associated with the submission of results on the registry (Table 2).

Among the 218 applicable clinical trials, 8% (95% CI, 4-11%) reported results 12 months after the primary completion date. Median time to results submission on the registry for applicable clinical trials was 31.3 months (95% CI, 27.9-38.0) and unreached for non-applicable clinical trials (Supplementary Fig. S1).

## Discussion

In our work, 386 (70%) PDAC trials had available results (submitted on the registry and/or published in a full-text



**Figure 4.** Cumulative probability of trials submitting results on the ClinicalTrials.gov registry over time. The dotted curves represent the 95% confidence intervals. The vertical dotted line represents the 12 months cut-off.

article). Applicable clinical trials were more likely to have available results and to submit results on the registry.

Our work is the first to study results availability in a large sample of trials evaluating PDAC management. Non-availability of results is an important issue with an ethical burden.<sup>9,10</sup> First, older studies have already reported a tendency to less publish trials with negative results, creating a risk of biased literature.<sup>12,13</sup> Fortunately, several journals specifically focus on publishing negative results.<sup>18</sup> In 2014, The Oncologist has launched the “Clinical Trial section” committed to publishing clinical trials even with negative outcomes.<sup>19</sup> Second, we estimated that 6 436 (17%) patients were involved in PDAC trials without available results. We also found that terminated and small-sample size trials were less likely to have available results, creating the risk of repeating an inefficient trial (due to slow accrual or toxicity or other reasons). Encouragingly, applicable clinical trials, covered by the 2007 FDAAA 801 and 2017 final rule, were more likely to have available results.

It had previously been shown that, following trial registration on ClinicalTrials.gov, about 50% of randomized drug trials do not publish their results.<sup>20</sup> Similar findings have also been observed for oncology trials specifically.<sup>21-25</sup> In other words, registration alone has failed to guarantee the availability of results over time.

In our work, only 42% of trials had published their results in a full-text article 36 months after the primary completion date. We did not consider results only published in abstracts because previous evidence has suggested that the quality of abstracts in oncology meetings is often suboptimal.<sup>26</sup> Publication of results in journals is a time-consuming process, especially in case of multiple rejections. Submitting results to the registry is a way to avoid this delay. We observed that only 28% of trials in our work had submitted results on ClinicalTrials.gov 36 months after their primary completion date. As required by the 2007 FDAAA 801 and its final rule, applicable clinical trials were more compliant with results submitted on the registry. Previous studies have shown poor compliance with this act.<sup>17,27,28</sup> Similarly, a recent work showed that less than 50% of applicable clinical trials reported results on EudraCT.<sup>29</sup> Our work suggests either

**Table 2.** Trial characteristics associated with results availability and submission of results on the registry (multivariable analysis).

	Availability of results	Submission on the registry
Design Randomized (vs. non-randomized)	HR = 1.01 (95% CI, 0.80-1.27), <i>P</i> = .96	HR = 0.92 (95% CI, 0.66-1.27), <i>P</i> = .61
Type of funding Industry and mix (vs. non-industry)	HR = 0.73 (95% CI, 0.59-0.91), <i>P</i> = .005	HR = 0.76 (95% CI, 0.57-1.02), <i>P</i> = .064
Status Terminated (vs. completed)	HR = 0.51 (95% CI, 0.39-0.67), <i>P</i> < .001	HR = 1.12 (95% CI, 0.82-1.53), <i>P</i> = .48
Study phase Phase II/III, III, and IV (vs. the rest)	HR = 0.68 (95% CI, 0.41-1.10), <i>P</i> = .11	HR = 0.73 (95% CI, 0.36-1.47), <i>P</i> = .38
Sample size of enrollment (per 10 patients)	HR = 1.02 (95% CI, 1.01-1.03), <i>P</i> = .003	HR = 1.01 (95% CI, 1.00-1.03), <i>P</i> = .10
Applicability <sup>a</sup> Applicable (vs. non-applicable)	HR = 2.13 (95% CI, 1.73-2.63), <i>P</i> < .001	HR = 13.37 (95% CI, 9.24-19.36), <i>P</i> < .001

<sup>a</sup>Applicability regarding the 2007 Food and Drug Administration Amendments Act 801 and its final rule was defined in the Methods section

an improvement of this requirement or higher compliance in some research fields. Nevertheless, only 8% of applicable clinical trials in our sample complied with the requirement of submitting results within one year after the primary completion date. Again here, despite the establishment of an explicit sanction,<sup>16</sup> the 2007 FDAAA 801 and its final rule seem insufficient to guarantee results submission on the registry in the required delay. As mentioned by De Vito et al., this could be explained by the absence of any enforcement actions by regulators with no history of fines imposed by the FDA to date.<sup>17</sup> Contrarily to previous findings, there was no association between trial funding and reporting of results on the registry in our work.<sup>17,21,27</sup>

Not having access to trial results creates an even greater burden for rare and aggressive diseases such as PDAC for which trials can be hard to conduct although new therapeutics are urgently needed. Few new drugs have gained recent approval for PDAC treatment.<sup>30,31</sup> Therefore, there is an urgent need to find new ways to improve results availability. Considering that an open public audit of compliance could help with results reporting, De Vito et al. have established an openly accessible public website [fdaaa.trialstracker.net](http://fdaaa.trialstracker.net) where data on compliance with the 2007 FDAAA 801 and final rule is updated on a daily basis. Furthermore, one study has shown that sending email reminders to applicable clinical trials significantly improved the submission of results on the registry at six months.<sup>32</sup> Finally, enhancing awareness of results availability among investigators and oncology groups who promote and conduct trials might be another solution.

Our work has various limitations. First, we only considered trials registered on ClinicalTrials.gov to have a homogeneous extraction of the data and cannot extrapolate to other registries. However, it is currently the largest registry.<sup>15</sup> Then, we had to rely on the accuracy of data on the registry which is not always up to date and/or of high quality.<sup>15</sup> Indeed, we found that 45 trials had results available before the declared primary completion date and only 51% of trials were prospectively registered. Of note, US law requires trial registration within 21 days of first patient enrollment which could also partly explain this previous result. This quality issue might have also impacted our identification of applicable clinical trials. Furthermore, competing interpretations of the 2007 FDAAA 801 over the years have created confusion over which trials were required to report; the final rule implemented on 18

January 2017 has clarified this point.<sup>16</sup> Therefore, with the data at hand, some clinical trials might have been wrongly considered applicable in our work. Also, we found 24 (24/218 = 11%) submitted certifications that we did not include in our analysis which may have underestimated compliance with the FDAAA 801. On a different note, we also evaluated trials with a non-therapeutic purpose or studying interventions other than drugs or biological products. One could argue that unavailable results for these trials might not have the same impact on the waste in research. Indeed, some interventions, such as behavioral interventions or medical devices, are probably less likely to be repeated in case of failure even in the absence of published results. Nevertheless, most trials in our sample had a treatment purpose and studied drugs or biological products. Finally, some full-text articles could have been missed since identification has been done by one reviewer and only one database (MEDLINE) has been searched.

## Conclusion

It is crucial to help improve the availability of results for future trials in patients with PDAC since it will become an important public health issue. New ways to improve results availability are urgently awaited.

## Funding

This work received no funding.

## Conflict of Interest

The authors indicated no financial relationships.

## Author Contributions

Conception/design: A.P., P.R., I.B. Provision of study material or patients: A.P. Collection and/or assembly of data: A.P. Data analysis and interpretation: A.P., I.B. Manuscript writing: A.P. Final approval of manuscript: All authors.

## Data Availability

The data underlying this article are available in Zenodo at <https://doi.org/10.5281/zenodo.5886999>.

## Supplementary Material

Supplementary material is available at *The Oncologist* online.

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